

SELECTED NEUROPHARMACOLOGY OF RESURGENCE

by

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ABSTRACT

Selected Neuropharmacology of Resurgence

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Resurgence refers to the reappearance of an extinguished operant behavior when reinforcement for an alternative behavior is also discontinued. It is especially relevant to the reappearance of problem behavior because many behavioral interventions discontinue reinforcement for aberrant behavior while simultaneously reinforcing an appropriate response. Existing information about the neuropharmacology of resurgence is scarce, but suggests overlap between drug seeking observed in the resurgence model and drug seeking observed in the more widely studied reinstatement and renewal models. The aim of this dissertation was to explore additional neural systems relevant to reinstatement and renewal preparations within a resurgence paradigm to assess further overlap. The neuropharmacology of resurgence was examined in two studies via administration of two drugs that have proven effective in blocking drug seeking in reinstatement and renewal preparations. In two experiments, rats earned food pellets for pressing

a target lever in Phase I. In Phase II, lever pressing no longer produced food, but food was delivered contingent on an alternative nose poke response. Finally in Phase III, neither response produced food deliveries. Prior to these Phase III sessions, separate groups of rats were injected with 0, 50, or 100 $\mu\text{g}/\text{kg}$ of the dopamine D_2 receptor antagonist raclopride in Experiment 1 or 0, 20, or 40 $\mu\text{g}/\text{kg}$ of α_2 agonist clonidine in Experiment 2. Both doses of raclopride were effective in blocking resurgence, but there was strong evidence that the higher dose did so via motor rather than motivational impairment. Furthermore, the lower dose significantly suppressed the alternative nose poke, which suggests motor impairment, as well. Only the higher dose of clonidine blocked resurgence, but did so with no evidence of motor impairment. Raclopride significantly impacted extinction of the alternative poke at both doses tested, whereas clonidine had no effect at either dose. The results of the present studies provide additional information about the neuropharmacology of resurgence, as well as additional evidence of overlap between resurgence, reinstatement, and renewal. The present results may also have implications regarding underlying neural mechanisms and for pharmacotherapies to attenuate relapse when alternative sources of reinforcement are thinned or discontinued.

(125 pages)

PUBLIC ABSTRACT

Selected Neuropharmacology of Resurgence

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The reemergence of problem behavior (i.e., relapse) is a key concern in most behavioral interventions. Resurgence refers to the reappearance of a previously rewarded behavior when reward for an alternative behavior is also discontinued. It is especially relevant to the reappearance of problem behavior because many behavioral interventions discontinue reward for aberrant behavior while simultaneously rewarding an appropriate response.

Understanding the underlying neuropharmacology of behavioral phenomena such as resurgence is important because it helps elucidate the neural processes at the root of such behavior, and also has implications for pharmacotherapies. Existing information about the neuropharmacology of resurgence is scarce, but suggests overlap between relapse observed in the resurgence model and relapse observed in the more widely studied reinstatement and renewal models. The aim of this dissertation was to explore additional neural systems relevant to reinstatement and renewal preparations within a resurgence paradigm to assess further overlap.

The neuropharmacology of resurgence was examined in two studies via administration of two drugs that have proven effective in blocking the reemergence of behavior in reinstatement and renewal preparations. In two experiments, rats were rewarded with food for pressing a target lever in Phase I. The lever no longer produced food in Phase II, but was delivered contingent on an alternative nose poke response. Finally in Phase III, neither response produced food deliveries. Prior to Phase III sessions, separate groups of rats were injected with various doses of the dopamine D₂ receptor antagonist raclopride in Experiment 1, or the α_2 agonist clonidine in Experiment 2.

Both raclopride and clonidine dose-dependently attenuated the reemergence of the target lever press. However, there was evidence that raclopride may have impacted motor behavior at both doses, whereas rats treated with clonidine showed no such deficits. Raclopride also significantly impacted rate of decline of the alternative poke at both doses tested, whereas clonidine had no effect at either dose.

The results of the present studies provide additional information about the neuropharmacology of resurgence, as well as additional evidence of overlap between resurgence, reinstatement, and renewal. These results have implications regarding underlying neural mechanisms and pharmacotherapies to attenuate relapse when alternative sources of reinforcement are thinned or discontinued.

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CHAPTER I

INTRODUCTION

Resurgence is a behavioral phenomenon in which extinguished operant behavior reappears at the onset of extinction of an alternative response (Epstein, 1983). Differential reinforcement of alternative (DRA) behavior procedures, in which the reinforcing consequences of problem behavior are withheld while appropriate behaviors are reinforced, are a widely used and effective method of treatment (see Petscher, Rey, & Bailey, 2009). However, reduction or elimination of reinforcement for the alternative response tends to result in increased levels of the problem behavior (Volkert, Lerman, Call, & Trosclair-Lasserre, 2009). Thus, resurgence has applied importance because it describes relapse common to DRA-based behavioral interventions.

Reinstatement (Campbell, Phillips, Fixsen, & Crumbaugh, 1968; Rescorla & Skucy, 1969) and renewal (Bouton & Bolles, 1979) are two other behavioral phenomena that produce the reappearance of previously reinforced responding. Regarding relapse to problem behavior, both procedures have been widely used to model relapse to drug seeking in animal subjects. Reinstatement refers to extinguished responding that reoccurs despite continued absence of drug upon re-exposure to the previously self-administered drug, drug-associated cues, or stress (see Shaham, Shalev, Lu, de Wit, & Stewart, 2003). Renewal refers to drug seeking that occurs when contextual changes accompany changes in drug availability: Drug-

maintained responding is trained in one distinct context, extinguished in a different context, and then increases when the subject is reintroduced to the original self-administration context (see Crombag, Bossert, Koya, & Shaham, 2008).

Although resurgence may pose a significant risk for relapse within applied settings in which alternative reinforcement is used, little is known about the underlying neuropharmacology of resurgence. Quick, Pyszczynski, Colston, and Shaham (2011) found that administration of the dopamine D₁ receptor antagonist SCH 23390 blocked resurgence of cocaine seeking. Dopamine D₁ receptor activation also plays a critical role in various types of reinstatement and renewal of drug seeking (e.g., Alleweireldt, Weber, Kirschner, Bullock, & Neisewander, 2002; Capriles, Rodaros, Sorge, & Stewart, 2003; Crombag, Grimm, & Shaham, 2002; Norman, Norman, Hall, & Tsibulsky, 1999), so the Quick et al. results indicate common neuropharmacology among the models of relapse to drug seeking.

Considerably more is known about the neuropharmacology of reinstatement and renewal (see Crombag et al., 2008; Bossert, Ghitza, Lu, Epstein, & Shaham, 2005; Shalev, Grimm, & Shaham, 2002). If resurgence shares common neurobiology with these models, as the Quick et al. (2011) data suggest, then other neural systems critical in reinstatement and renewal may also be critical to resurgence. The purpose of the present dissertation is to investigate the role of some of these neural systems that have been shown to play a substantial role in the drug seeking observed in various types of reinstatement and renewal models.

The dopamine D₂ receptor is linked to drug-induced reinstatement (e.g., Shaham & Stewart, 1996), cue-induced reinstatement (e.g., Liu & Weiss, 2002b; Tobin, Newman, Quinn, & Shalev, 2009), and renewal (Crombag et al., 2002). Because the D₂ receptor has not yet been studied in resurgence, and because of its importance in reinstatement and renewal, it was studied in Experiment 1. Resurgence has been likened to stress-induced relapse (Quick et al., 2011), but the dopamine D₂ receptor does not appear to play a role in stress-induced reinstatement (Capriles et al., 2003; Shaham & Stewart, 1996; Tobin et al., 2009). The adrenergic α_2 receptor, however, has been heavily implicated in stress-induced reinstatement (Erb et al., 2000; Lê, Harding, Juzytsch, Funk, & Shaham, 2005; Shaham, Highfield, Delfs, Leung, & Stewart, 2000; Zislis, Desai, Prado, Shah, & Bruijnzeel, 2007), but has not yet been examined in resurgence, so it was the target of Experiment 2.

The role of D₂ and α_2 receptors in resurgence was examined via administration of the dopamine D₂ antagonist raclopride and the adrenergic α_2 receptor agonist clonidine. Separate groups of rats pressed a target lever for food deliveries during Phase I. In Phase II, the lever press was extinguished while an alternative nose poke response was reinforced with food deliveries. Finally in Phase III, the alternative poke response was also placed on extinction while the target lever press remained on extinction. Prior to Phase III sessions the groups of rats received injections of 50 or 100 $\mu\text{g}/\text{kg}$ of raclopride, 20 or 40 $\mu\text{g}/\text{kg}$ of clonidine, or saline.

Raclopride and clonidine dose-dependently attenuated resurgence of target lever pressing during Phase III. Both doses of raclopride, but only the higher dose of clonidine reduced resurgence to levels statistically indistinguishable from the end of Phase II. A variety of measures were examined to rule out the possibility that the drugs reduced resurgence via motor impairment. There was evidence that both doses of raclopride may have impaired motor function, whereas there was no evidence of motor impairment within the animals treated with clonidine.

The present study showed that D_2 and α_2 receptors are critical to resurgence, providing further evidence of common neurobiology among commonly used models of drug seeking. These results provide additional information about the neural mechanisms mediating resurgence, and also have implications for the development of pharmacotherapies that may be used in conjunction with behavioral interventions to reduce the likelihood of relapse.

CHAPTER II
REVIEW OF LITERATURE

Reduction of Problem Behavior

Reduction of problem behavior is the primary aim of many behavioral interventions. Extinction, which refers to the withdrawal of contingent reinforcement for behavior, is a widely used behavioral intervention (see Lerman & Iwata, 1996). Although effective in reducing targeted behaviors, extinction is seldom used in isolation. An additional treatment component in which an alternative, appropriate response is reinforced in conjunction with extinction of the problematic behavior is typically used. Reinforcement of alternative behaviors in this manner is outlined as a necessary practice in the Guidelines for Responsible Conduct for Behavior Analysts, developed by the Behavior Analyst Certification Board (BACB) who is responsible for certifying behavior analysts (BACB, 2010).

Extinction used in isolation can also produce undesirable side effects. For instance, an extinction burst may occur, which is a temporary increase in the frequency, duration, or intensity of a response that has been placed on extinction (Cooper, Heron, & Heward, 2007). Such increases may be undesirable when dealing with especially severe problem behavior. Extinction bursts are observed less frequently when extinction is employed in concurrence with reinforcement for alternative behaviors than when used in isolation (see Lerman & Iwata, 1995). In addition to quickly reducing problem behavior with minimal side effects, these

treatments are effective in addressing a number of problem behaviors and have the added benefit of training appropriate alternate behaviors (see Petscher et al., 2009). Procedures that provide reinforcement for an alternative response in conjunction with extinction of another behavior are broadly referred to as DRA behavior procedures (Cooper et al., 2007).

An example of a DRA-based treatment used to eliminate problem behavior is functional communication training (FCT; Carr & Durand, 1985). Within FCT, clinicians first identify the reinforcer maintaining problem behavior. The reinforcer maintaining problem behavior is then withheld (i.e., extinction) and an alternative communicative response is trained and maintained by contingent delivery of that same reinforcer, or by a reinforcer in the same class. When implemented properly, FCT is effective in addressing a variety of problem behaviors (Tiger, Hanley, & Bruzek, 2008).

A second form of DRA treatment primarily used to curb drug abuse is called Contingency Management (Bigelow, Stitzer, Griffiths, & Liebson, 1981). The treatment provides nondrug incentives contingent on abstaining from drug use, confirmed via drug testing. A variety of nondrug incentives, such as vouchers with monetary value (Silverman, Chutuape, Bigelow, & Stitzer, 1999) or access to work opportunities (Silverman, Svikis, Robles, Stitzer, & Bigelow, 2001), are effective reinforcers of abstinence within the treatment. When the appropriate drug tests are used at regular intervals, Contingency Management is effective in decreasing drug

use and preventing relapse to a number of different drugs of abuse (see Prendergast, Podus, Finney, Greenwell, & Roll, 2006)

Despite the beneficial outcomes associated with DRA treatments, the risk of relapse for problem behavior is high if alternative reinforcement for the adaptive behavior is discontinued or reduced (Volkert et al., 2009). Increases in problem behavior inflate the likelihood that problem behavior will contact reinforcement and will be maintained, posing a serious threat to treatment efficacy and durability. Thus, this type of relapse is a primary concern in treatments employing DRA methods.

Resurgence

Resurgence refers to the reappearance of an extinguished response when reinforcement for an alternative response is also discontinued (Epstein, 1983). In laboratory experiments on resurgence, the procedure generally consists of three phases. First, a response (Response 1) is trained and maintained via contingent reinforcement. Next, Response 1 is placed on extinction, resulting in decreased levels of that response, while an alternative response (Response 2) is introduced and reinforced. Finally, Response 2 is also extinguished, and despite continued extinction, Response 1 increases in frequency at the onset of extinction of the alternative response.

Because resurgence refers to reappearance of past behaviors when reinforcement for alternative behaviors is withheld, it is especially relevant to relapse observed under DRA-based treatments. In applied settings, the problematic behavior is analogous to Response 1 while the adaptive behavior is like Response 2. As a behavioral intervention, reinforcement is discontinued for the problem behavior while delivered contingent on an appropriate response. If for any reason reinforcement of the appropriate response ceases, problem behavior tends to reoccur. The role of resurgence in relapse of behaviors treated via DRA interventions has been suggested by a number of authors (Doughty & Oken, 2008; Lattal & St. Peter Pipkin, 2008; Shahan & Sweeney, 2011).

Volkert and colleagues (2009) specifically examined resurgence within an FCT treatment used to address problem behavior in children with autism or developmental disabilities. Experimenters first determined the reinforcer maintaining problem behavior of each child participating in the study. Then, in conjunction with discontinuation of reinforcement maintaining problem behavior, the children were then taught to request that reinforcer via an alternative communicative response, and this communicative response was reinforced for a number of sessions. Finally, neither problem behavior nor the new adaptive response was reinforced. Volkert and colleagues tested the effects of discontinuing (Experiment 1) and reducing reinforcement (Experiment 2) for the alternative communicative response, and found that problem behavior increased above levels observed during FCT in both cases.

In a similar preparation, Wacker et al. (2011) examined the durability of an FCT treatment for children displaying destructive behavior. FCT was used to decrease the destructive behavior within the study, and periodic extinction probes were conducted to determine whether destructive behavior reemerged under circumstances in which neither the destructive nor alternative responses were reinforced. Wacker and colleagues reported increases in destructive behavior during early extinction probes, but the increases were attenuated as the children were exposed to more of the FCT treatment. These increases in problem behavior during extinction probes, and subsequent decreases in magnitude of those increases with longer exposure to treatment, were well described by a quantitative model of resurgence proposed by Shahan and Sweeney (2011).

Relapse to Drug Seeking

As noted earlier, Contingency Management is a DRA-based intervention for drug abuse in which individuals submit to regular drug testing and are provided with nondrug incentives contingent on negative drug tests (Bigelow et al., 1981). Resurgence-like mechanisms may also be relevant to relapse to drug taking within Contingency Management treatments in that drug use tends to increase once the treatment ends and nondrug alternatives are no longer provided. For instance, Silverman et al. (1999) reported dramatic relapse to cocaine taking once the treatment was discontinued. Furthermore, a meta-analysis on Contingency

Management reported a downward trend in effect size as time increased after treatment cessation (Prendergrast et al., 2006).

There is also evidence that other events that can be interpreted as instances of alternative reinforcement loss can cause relapse. For instance, job loss and divorce are associated with increased likelihood of relapse (Falba, Teng, Sindelar, & Gallo, 2005; Gallo, Bradley, Siegel, & Kasl, 2001; San Jose, Van Oers, Van De Mheen, Garretsen, & Mackenbach, 2000; Temple, Fillmore, Hartka, Johnstone, Leino, & Motoyoshi, 1991). Based on findings such as these, the resurgence procedure has been applied as a model of relapse to drug seeking to determine whether loss of nondrug reinforcement produces relapse of extinguished drug seeking (Podlesnik, Jimenez-Gomez, & Shahan, 2006; Quick et al., 2011).

Podlesnik and colleagues (2006) provided the first demonstration of resurgence as an animal model of drug relapse. In the study, rats first pressed a lever for alcohol deliveries during baseline sessions. Next, alcohol deliveries were discontinued resulting in decreased lever pressing. Concurrent with introduction of the extinction contingencies on the lever, a chain pull response was made available that produced food pellet deliveries. When the chain pull was also extinguished, lever pressing increased despite the continued absence of alcohol deliveries. Thus, Podlesnik et al. showed that loss of alternative nondrug reinforcement is capable of producing relapse of extinguished drug seeking.

Quick and colleagues (2011) extended the resurgence procedure to model relapse of extinguished cocaine seeking. This study not only extended resurgence to

another drug of abuse, but also ruled out an alternative interpretation of the Podlesnik et al. (2006) data that rats may have been seeking alcohol for its caloric value: Resurgence of cocaine seeking could not be interpreted as calorie seeking because cocaine has no caloric value. In the Quick et al. study, one group of rats initially lever-pressed for cocaine deliveries, followed by extinction of lever pressing and food delivered contingent on an alternative nose poke response. Quick and colleagues found that cocaine seeking did in fact resurge when food pellets, introduced in parallel to discontinuation of cocaine, were also withheld. Therefore, discontinuation of nondrug reinforcement is capable of producing relapse to drug seeking, and resurgence appears to be a viable model of drug relapse.

Other Models of Relapse

Reinstatement (Campbell et al., 1968; Rescorla & Skucy, 1969) and renewal (Bouton & Bolles, 1979) are two other procedures that produce the reappearance of extinguished operant behavior (i.e., relapse). In terms of relapse to problem behavior, both reinstatement and renewal have been widely applied as models of relapse to drug seeking; however, only two studies have used resurgence as a model of drug relapse. Therefore, much of what is known in the basic literature about relapse to drug seeking, and its underlying neuropharmacology, comes from studies using these other two models.

Reinstatement is the most widely used model of relapse (see Shaham et al., 2003). Like resurgence, reinstatement is a three-phase procedure. First, an arbitrary response is trained and maintained by contingent drug deliveries. Second, that response is placed on extinction and contingent drug deliveries are withheld until the animal stops responding or responds at a low predetermined rate. Finally, exposure to certain stimuli results in increased levels of the previously drug-maintained response. The stimuli that reliably reinstate drug seeking include re-exposure to the previously self-administered drug (de Wit & Stewart, 1981), drug-associated cues (See, 2002; Weiss et al., 2001), or certain stressors (Shaham & Stewart, 1995). The widespread use of this model is likely based on the variety of stimuli that are used to induce drug seeking within the preparation.

Renewal, also a three-phase procedure, has recently gained popularity within the drug relapse literature (see Crombag et al., 2008). Renewal is a context-based manipulation in which drug availability changes as a function of background contextual stimuli (Crombag et al., 2002). First, drug is self-administered in the presence of one set of distinct contextual stimuli (e.g., olfactory, visual, and tactile). Next, the drug-maintained response is extinguished in the presence of a distinctly different set of stimuli until responding ceases or falls to a low level. Finally, the response previously maintained by drug increases in frequency upon return to the context in which drug was originally available.

Like resurgence, circumstances similar to those modeled in reinstatement and renewal preparations can produce relapse in human populations. For instance,

Chornock, Stitzer, Gross, and Leischow (1992) found that smoking four cigarettes subsequent to a four-day period of paid abstinence from smoking resulted in increased likelihood of relapse to smoking, relative to a group who was not forced to smoke cigarettes. Regarding cue exposure, exposure to drug associated cues increases craving (Childress et al., 1993), which is correlated with actual drug use (Tiffany, 1990). Stressful life events are also associated with drug taking and relapse (see Sinha, 2001). Finally, contextual change also appears to produce relapse in human drug users in that individuals can successfully abstain from drug use in inpatient detoxification programs, but tend to relapse once they return to their home environments (Hunt, Barnett, & Branch, 1971).

Selected Neuropharmacology

The Quick et al. (2011) study described earlier also examined the role of dopamine D₁ receptors in resurgence of cocaine seeking. Quick and colleagues injected a separate group of animals with the dopamine D₁ antagonist SCH 23390 prior to resurgence sessions and found that antagonism of D₁ receptors blocked resurgence of cocaine seeking. Dopamine D₁ receptor antagonism also blocks drug seeking in certain types of reinstatement preparations (e.g., Alleweireldt et al., 2002; Capriles et al., 2003; Norman et al., 1999) and in renewal preparations (Crombag et al., 2002), so the Quick et al. results provide preliminary evidence that resurgence

shares common neuropharmacology with drug seeking observed in these other two models.

A considerable amount of research has investigated the neuropharmacology of drug seeking in reinstatement (see Bossert et al., 2005; Shalev et al., 2002) and renewal preparations (see Crombag et al., 2008), but only Quick et al. (2011) have attempted such a study with the resurgence model. Because dopamine D₁ antagonists block relapse to drug seeking in reinstatement and renewal preparations, attenuation of resurgence by SCH 23390 in the Quick et al. study suggests overlapping neuropharmacology of resurgence, reinstatement, and renewal. Therefore, other neural systems implicated in reinstatement and renewal may also play a role in resurgence.

Dopamine D₂ Receptors

There are five known types of dopamine receptors: D₁-5 (Vallone, Picetti, & Borrelli, 2000). The dopamine D₁-like family of receptors (D₁ and D₅ receptors) increases cyclic adenosine monophosphate (cAMP) concentrations while the D₂-like family (D₂-D₄ receptors) inhibits cAMP formation; cAMP formation is necessary for amplification of intracellular signaling (Vallone et al., 2000). Drug abuse and relapse research has generally focused on the involvement of dopamine D₁-D₃ receptor subtypes due to their distribution within relevant brain systems and availability of selective ligands (Heidbreder & Newman, 2010; see Self, 2010).

As noted earlier, Quick et al. (2011) found that the dopamine D₁ receptor antagonist SCH 23390 blocks resurgence of cocaine seeking. Dopamine D₁ receptors also appear to play a role in various types of reinstatement (Alleweireldt et al., 2002; Capriles et al., 2003; Norman et al., 1999), as well as renewal of drug seeking (Bossert, Poles, Wihbey, Koya, & Shaham, 2007; Crombag et al., 2002; Hamlin, Blatchford, & McNally, 2007). The dopamine D₂ receptor also appears to play a significant role across different models of relapse. Systemic administration of dopamine D₂ antagonists blocks reinstatement induced by re-exposure to the previously self-administered drug (Ettenberg, 1990; Khroyan, Barrett-Larimore, Rowlett, & Spealman, 2000; Schenk & Gittings, 2003; Shaham & Stewart, 1996; but see Carati & Schenk, 2011). Dopamine D₂ antagonists also appear to block renewal of drug seeking (Crombag et al., 2002), and reinstatement produced by exposure to both discrete (Gál & Gyertyán, 2006; Liu et al., 2010; Tobin et al., 2009) and discriminative cues (Cervo, Carnovali, Stark, & Mennini, 2003; Liu & Weiss, 2002b; but see McFarland & Ettenberg, 1997).

Stress-induced reinstatement, however, does not appear to be mediated by activation at dopamine D₂ receptors. Systemic administration of dopamine D₂ antagonists has no effect on footshock- (Shaham & Stewart, 1996) or food deprivation-induced (Tobin et al., 2009) relapse to heroin seeking. Furthermore, localized injections of D₂ antagonist drugs within the prelimbic prefrontal cortex and orbitofrontal cortex have no effect on footshock-induced reinstatement of cocaine seeking (Capriles et al., 2003).

Similar patterns emerge in the results of studies that have examined relapse to food seeking. Administration of a dopamine D₂ antagonist blocks food-primed reinstatement in a runway task (Chausmer & Ettenberg, 1997; Horvitz & Ettenberg, 1988). Interestingly, there is evidence that D₂ antagonists potentiate (Ball, Combs, & Beyer, 2011) or have no effect on discrete cue-induced reinstatement of food seeking (Gál & Gyertyán, 2006), but appear to block renewal of food seeking (Rauhut, Fenton, & Bardo, 2010). To my knowledge, no studies have yet examined how D₂ antagonists affect stress-induced reinstatement of food seeking.

The results of studies examining the role of dopamine D₂ antagonism with respect to drug seeking largely mirror those of D₁ receptor antagonism with the exception of stress-induced reinstatement. If resurgence, renewal, and drug- and cue-induced reinstatement models share common neuropharmacology, then D₂ receptor antagonists should have some effect on resurgence.

Adrenergic α_2 Receptors

Norepinephrine levels typically increase in response to various stressors (Bremner, Krystal, Southwick, & Charney, 1996), and accordingly, adrenergic transmission has been one of the primary neuropharmacological targets in research on stress-induced reinstatement (see Shaham, Erb, & Stewart, 2000).

Administration of α_2 agonists blocks shock-induced reinstatement of cocaine (Erb et al., 2000), heroin (Shaham et al., 2000), alcohol (Lê et al., 2005), and nicotine seeking (Zislis et al., 2007). Comparable results have been reported with chemical

stressors. For instance, clonidine blocks yohimbine-induced reinstatement of cocaine (Lee, Tiefenbacher, Platt, & Spealman, 2003; but see Brown, Tribe, D'souza, & Erb, 2009), and alcohol seeking (Lê, Funk, Harding, Juzytsch, & Fletcher, 2009).

The effects of clonidine on drug-primed reinstatement are somewhat less conclusive. Erb and colleagues (2000) reported that the α_2 adrenergic receptor agonists clonidine, lofexidine, and guanabenz did not impact drug-primed reinstatement of cocaine seeking. Platt, Rowlett, and Spealman (2007) reported that clonidine attenuated drug-primed reinstatement, but their experimental arrangement included elimination of cocaine-paired cues during extinction and subsequent reintroduction during reinstatement; therefore, it is not entirely clear if clonidine blocked cue-induced or drug-induced reinstatement. Considering Erb et al. (2000) tested three different α_2 agonists and each was ineffective in blocking drug-primed reinstatement, it seems unlikely that α_2 receptors are involved in drug-induced reinstatement. However, α_2 receptors may play a role in cue-induced reinstatement in light of the results from Platt et al. (2007).

The existing evidence regarding the effects of α_2 agonists on cue-induced reinstatement are conflicting. Highfield, Yap, Grimm, Shalev, and Shaham (2001) reported that lofexidine was ineffective in reducing cue-induced reinstatement; however, lofexidine injections were not limited to reinstatement sessions and were administered during a portion of the baseline sessions, as well as all extinction and reinstatement sessions. Therefore, it is difficult to say whether the prolonged exposure to the drug may have impacted their results. However, Buffalari, Baldwin,

and See (2012) reported that early exposure to guanfacine during extinction attenuated subsequent yohimbine-induced reinstatement, which suggests that prolonged exposure could make the drug even more effective at reducing reinstatement. In what may be the most convincing demonstration of α_2 agonists attenuating cue-induced reinstatement, Smith and Aston-Jones (2011) reported that the α_2 agonists clonidine, UK-14,304, and guanfacine decreased cue-induced reinstatement of cocaine seeking when administration was limited only to reinstatement sessions.

Few studies have examined the effects of α_2 agonists on relapse to food seeking, but various α_2 agonists have shown to be ineffective in reducing yohimbine-induced reinstatement of food seeking (Lê et al., 2011; Nair, Adams-Deutsch, Epstein, & Shaham, 2009). It is worth noting that yohimbine is a relatively unique stressor in that more commonly used stressors (e.g., shock) do not produce relapse to food seeking (Ahmed & Koob, 1997), whereas yohimbine does (Ghitza, Gray, Epstein, Rice, & Shaham, 2006).

Like dopamine D₂ receptors, adrenergic α_2 receptors appear to be involved in more than one type of relapse. Although α_2 agonists do not appear to impact priming reinstatement, and have not yet been tested in renewal arrangement, there is evidence that they are involved in both stress- and cue-induced reinstatement. Therefore, it is likely that these receptors are involved in resurgence, as well.

CHAPTER III

EXPERIMENT 1: THE ROLE OF DOPAMINE D₂ RECEPTORS IN RESURGENCE

Purpose

Resurgence procedures in which extinction of an alternative response produces the reappearance of an extinguished response are especially relevant in clinical relapse, but little is known about the neuropharmacology of resurgence except that dopamine D₁ receptors appear to play a critical role. Dopamine D₁ receptors are also involved in reinstatement and renewal preparations, suggesting common neurobiology. The dopamine D₂ receptor is also implicated in reinstatement and renewal, but has not yet been examined in resurgence. Thus, the role of dopamine D₂ receptors in resurgence was examined via administration of a dopamine D₂ receptor antagonist raclopride.

Rats responded in a resurgence procedure in which a target lever press produced food deliveries during Phase I, the lever press was then placed on extinction while an alternative nose poke produced food deliveries during Phase II, and finally the alternative nose poke was also placed on extinction while the target lever remained on extinction. Separate groups of animals were injected with vehicle or one of two doses of the dopamine D₂ receptor antagonist raclopride prior to each of the five Phase III sessions. Responding was compared in the last Phase II and first Phase III sessions, as well as across Phase III sessions, to explore the effects of raclopride on resurgence. The results of the study provide valuable information

regarding the underlying neural mechanisms of resurgence, which has seen little attention in the relapse literature, relative to reinstatement and renewal.

Method

Subjects

Twenty-four experimentally naïve male Long-Evans rats (Charles River, Portage, Michigan, USA) approximately 90 days old upon arrival in the experimental facility were used in the experiment. The animals' free-feeding weights were established over a period of approximately 14 days after arrival in the experimental facility. Subsequently, rats were maintained via supplemental feedings at approximately 80% of their free-feeding weights throughout the experiment. Rats were housed individually with free access to water in a temperature-controlled room with a 12:12h light/dark cycle (lights on at 7:00 AM). Experimental sessions took place at approximately the same time each day during the light cycle.

Apparatus

MED-Associates (1999) programming and interface controlled all experimental events and data recording. Four MED-Associates modular operant chambers (30 cm × 24 cm × 21 cm) housed in sound-attenuating cubicles were used. The chambers were composed of two Plexiglas walls, and two aluminum walls opposite one another. On the back wall of all chambers were five evenly spaced apertures, each containing a yellow light emitting diode (LEDs), as well as a

photobeam capable of detecting head entries (i.e., nose pokes). Centered on the opposite wall was a recessed receptacle (5 cm × 5 cm) in which 45-mg pellets were delivered. Pellet deliveries were accompanied by an audible click and lit receptacle. Levers to the left and right of the pellet receptacle were retractable, and above each of those levers was a lamp (2.5 cm diameter). Each chamber was also equipped with a house light for general illumination, as well as a Sonalert (2900± 500 Hz, 75–85 dB) for producing tones.

Drug

The dopamine D₂ receptor antagonist raclopride was used. Separate groups of animals ($n = 8$) received 0 (vehicle), 50, or 100 µg/kg of the drug. These doses have been used in previous studies to attenuate renewal (Crombag et al., 2002) and cue-induced reinstatement (Liu & Weiss, 2002b; Tobin et al., 2009), but not stress-induced reinstatement (Tobin et al., 2009). Raclopride was dissolved in a sterile 0.9% saline solution. Saline or raclopride was administered subcutaneously at an injection volume of 1 ml/kg 20 minutes prior to experimental sessions.

Procedure

Training. Rats experienced a single 30-min session of magazine training in which pellets were delivered according to a variable time (VT) 60-s schedule. The levers were extended into the chambers, but the lever lights and house lights remained off. An audible click and 3-s illumination of the pellet receptacle

accompanied pellet deliveries during training and throughout the experiment. In two additional sessions, pellets were available for lever pressing according to fixed ratio (FR) 1 schedule. One lever produced pellets when pressed (i.e., the target lever), while the other lever had no programmed consequences (i.e., inactive lever). The light above the target lever was lit and the location of the target lever (left or right) was counterbalanced across subjects.

Phase I. During Phase I, pellets were delivered contingent on target lever presses according to a variable interval (VI) 45-s schedule in 30-min sessions timed exclusive of 3-s pellet deliveries. Phase I lasted 20 sessions. At the end of Phase I, rats were assigned to one of two experimental groups ($n = 8$ per raclopride dose) or the control group ($n = 8$) while matching for mean response rates during the final 3 sessions of Phase I. Each drug dose was examined within a separate group of animals based on previous findings demonstrating variations across repeated resurgences (Lieving & Lattal, 2003).

Phase II. Next, lever presses were extinguished and no longer produced pellet deliveries. Occurring in conjunction with extinction of the lever press, the center nose poke at the rear of the chamber was lit because it was equidistant from the left and right levers. The first head entry into this poke in the first session of Phase II resulted in a pellet delivery, and afterward pellets were delivered according to a VI 10-s schedule. These contingencies remained in effect for 10 sessions, and were identical for all groups.

Phase III. During the next five sessions, both the lever and poke responses were extinguished and had no programmed consequences for all groups. As noted earlier, the groups received subcutaneous injections of 0 (vehicle), 50, or 100 $\mu\text{g}/\text{kg}$ raclopride 20 min prior to Phase III sessions.

Results

Phase I

All animals acquired the target lever press response during training sessions, and responding proceeded normally throughout Phase I. Subjects were then assigned to one of three treatment groups (0, 50, or 100 μg raclopride) so as to match average (last 3) baseline response rates on the target lever across groups. The top portion of Table 1 displays mean (Standard Error of the Mean; SEM) target (lever associated with food during Phase I), inactive (lever never associated with food), alternative (center poke associated with food during Phase II), and other (4 pokes never associated with food) response rates (responses per minute), as well as reinforcer rates for the three treatment groups across the final 3 Phase I sessions. Rates on the target lever did not vary systematically across groups, $F(2,21) = 0.00$, $p = 1.00$, and all other responses occurred similarly at low rates across the groups. Rates of food delivery also did not vary systematically across groups, $F(2,21) = .52$, $p = .600$, and were close to the programmed rate of reinforcement of 1.33 foods per minute.

Table 1

Mean (SEM) Response and Food Rates Averaged over the Final Three Sessions of Phase I and Phase II for Rats in Experiment 1

	Group		
	0 µg	50 µg	100 µg
Phase I			
Target	38.03 (10.31)	38.35 (6.54)	38.22 (7.04)
Alt	0.02 (0.01)	0.06 (0.04)	0.06 (0.03)
Inactive	1.15 (0.58)	1.38 (0.43)	1.02 (0.23)
Other	0.11 (0.04)	0.25 (0.17)	0.33 (0.19)
Foods	1.24 (0.02)	1.22 (0.01)	1.23 (0.01)
Phase II			
Target	2.53 (0.79)	2.29 (0.49)	1.63 (0.25)
Alt	50.93 (15.02)	65.61 (18.39)	49.14 (14.37)
Inactive	0.86 (0.33)	0.55 (0.13)	0.48 (0.13)
Other	7.43 (2.36)	4.49 (1.21)	6.25 (1.87)
Foods	4.70 (0.25)	4.57 (0.32)	4.62 (0.26)

Phase II

The bottom portion of Table 1 shows response and reinforcer rates averaged over the last 3 sessions of Phase II. The extinction contingencies in effect on the target lever reduced response rates to similarly low levels across groups, $F(2,21) = .71, p = .502$. Reinforcement of the alternative poke response was effective in increasing rates of responding, which were higher in the 50 µg group, but were not significantly different across groups, $F(2,21) = .32, p = .731$. Phase II was also associated with decreased rates of responding on the inactive lever, and increased

rates of response in the other pokes. The richer VI (10-s in Phase II versus 45-s in Phase I) produced more frequent reinforcement than in Phase I, and although the groups fell short of the programmed reinforcement rate of 6 pellets per minute, all groups earned comparable rates of pellet deliveries, $F(2,21) = .04, p = .943$.

Phase III

Resurgence in first Phase III session. Figure 1 shows the effects of raclopride on response rates in the first session of Phase III relative to the last session of Phase II. Data for the target lever, inactive lever, and all other nose pokes (i.e., the pokes that did not produce alternative reinforcers during Phase II) are displayed to demonstrate that the extinction contingencies introduced during Phase III produced food seeking (i.e., elevated responding on the target lever) rather than general activation (i.e., increased activity on responses with no prior history of reinforcement). Separate mixed model ANOVAs were conducted for each response with Phase as a within-subjects factor and Dose as a between-subjects factor.

The top panel of Figure 1 shows response rates on the target lever. With the exception of the 100 μg group, response rates were higher during Phase III, and raclopride dose-dependently reduced the amount of resurgence on the target lever. The mixed ANOVA supported this interpretation, yielding significant main effects of Phase, $F(1,21) = 11.61, p = .003$, and Dose, $F(2,21) = 5.75, p = .010$, as well as a significant interaction, $F(2,21) = 7.72, p = .003$. Fisher's Least Significant Difference (LSD) test indicated that the 0 and 100 μg groups differed significantly. To follow-up

the significant interaction, paired *t*-tests were performed to compare the effect of Phase at each Dose. These tests indicated that the significant interaction arose from significant resurgence occurring in the 0 μg group, $t(7) = -5.35$, $p = .022$, but neither the 50 μg group, $t(7) = -1.16$, $p = .286$, nor the 100 μg group, $t(7) = 1.59$, $p = .157$.

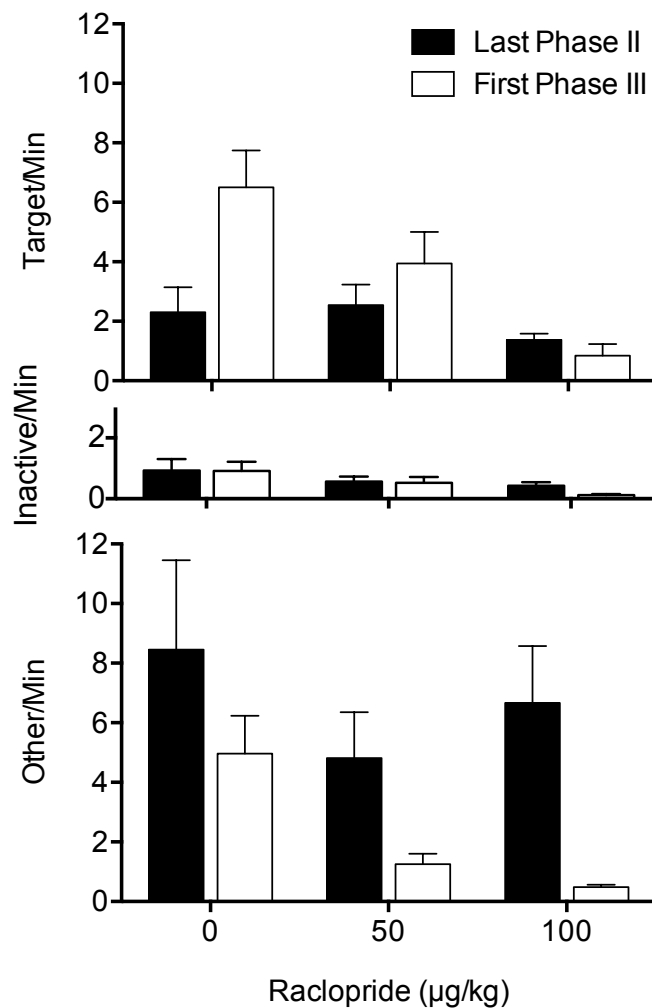


Figure 1. Effects of raclopride on mean (\pm SEM) response rates on the target lever (top panel), inactive lever (middle panel), and other pokes (bottom panel) within the last session of Phase II and first session of Phase III.

Thus, elimination of alternative reinforcement produced resurgence on the target lever, but only in the saline group, indicating that raclopride suppressed resurgence.

The middle and bottom panels of Figure 1 show response rates on the inactive lever and all other nose pokes, respectively. Again, these response rates were analyzed to rule out the possibility that resurgence on the target lever was accompanied by increases in responses with no history of reinforcement, indicative of general activation. The middle portion of Figure 1 shows response rates on the inactive lever. Inactive response rates were similar across groups and phases with the exception of the 100 μg group, which showed suppressed responding during Phase III. However, the mixed model ANOVA indicated that these differences were not significant, Phase $F(1,21) = 2.52, p = .127$, Dose $F(2,21) = 2.30, p = .125$, Interaction $F(2,21) = 1.44, p = .260$. Thus, Phase III was not associated with increased inactive lever pressing.

The bottom panel of Figure 1 shows response rates on all other nose pokes. Rates of responding in the other nose pokes were similar at the end of Phase II, and decreased during Phase III, which was supported by the mixed ANOVA yielding a significant main effect of Phase, $F(1,21) = 19.31, p < .001$. Although raclopride appeared to suppress rates of other pokes in the 50 and 100 μg groups relative to the 0 μg group, the main effect of Dose, $F(2,21) = 1.93, p = .170$, and the interaction, $F(2,21) = .77, p = .474$, did not reach significance. Unlike the inactive lever press, in which there was no significant change from Phase II to III, response rates to the other nose pokes decreased during Phase III. A similar effect was observed during

the transition from Phase I to II in that inactive lever presses decreased when the target lever press was extinguished. These results suggest that inactive presses and other pokes occurred because of generalization from the reinforced response (i.e., target lever in Phase I and alternative poke in Phase II).

Analysis of response rates on the target lever along with the two responses that never produced programmed consequences showed that resurgence during Phase III occurred only on the target lever, and only in the group of animals that did not receive raclopride injections. Therefore, raclopride effectively attenuated resurgence at both doses tested, 50 and 100 $\mu\text{g}/\text{kg}$.

Across Phase III sessions. Injections of saline (0 μg) or raclopride (50 or 100 μg) were administered before each of the five Phase III sessions, which allowed examination of whether repeated administration of raclopride alters the course of resurgence for the target lever or the course of extinction for the alternative poke. Figure 2 shows mean ($\pm\text{SEM}$) response rates for the target and alternative responses across all five sessions of Phase III. The top panel of Figure 1 shows the course of resurgence across sessions on the target lever. For the 0 μg group, target lever press rates declined steadily across Phase III sessions and were higher than either of the groups treated with raclopride. Rates for the 50 μg group were lower than that of the 0 μg , but also showed a different pattern across sessions in that the lowest rates occurred in Session 2, followed by recovery to levels near that of the 0 μg group by the end of Phase III. Response rates in the 100 μg group remained suppressed across Phase III sessions. A mixed ANOVA with Dose as a between-

subjects factor and Session as a repeated factor supported this interpretation, yielding significant main effects of Dose, $F(2,21) = 16.99, p < .001$, and Session, $F(4,84) = 14.92, p < .001$, as well a significant interaction, $F(8,84) = 4.34, p < .001$. Fisher's LSD test indicated each pair of groups differed significantly. The significant interaction arose from the effect of Session reaching significance within the 0 [$F(4,28) = 10.28, p < .001$] and 50 [$F(4,28) = 6.33, p = .001$], but not 100 μg group

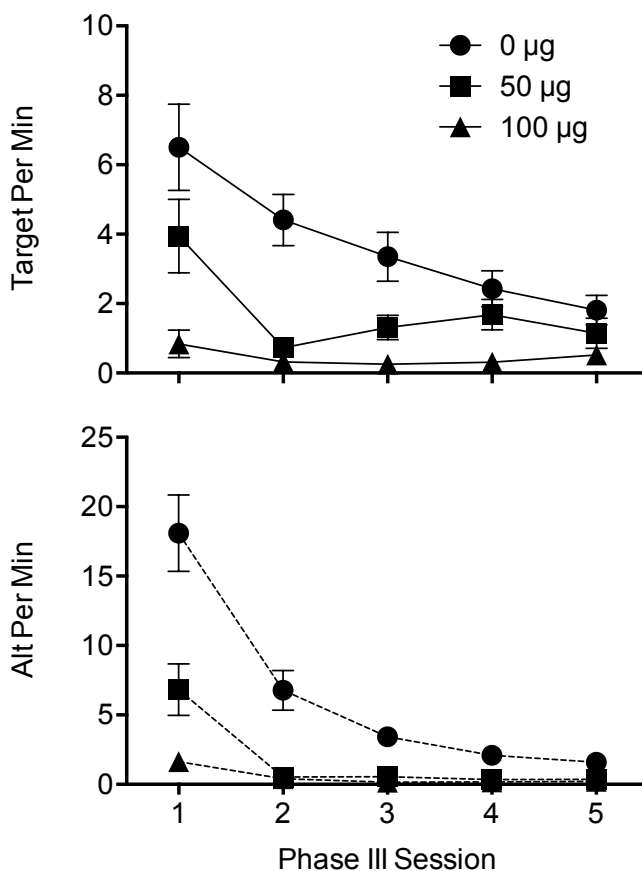


Figure 2. Effects of raclopride on mean (\pm SEM) response rates for the target lever (top panel) and alternative poke (bottom panel) across Phase III sessions.

[$F(4,28) = 1.07, p = .391$]. Furthermore, the effect of Dose was significant in sessions 1-4 (all p values $< .01$), but not Session 5 [$F(2,23) = 2.83, p = .08$].

Rates of nose poking across Phase III sessions are depicted in the bottom panel of Figure 2. Responding decreased across sessions for the 0 μg group, while raclopride dose-dependently reduced nose poking during the first session of Phase III, but appeared to suppress responding almost completely throughout the remaining sessions in both groups treated with raclopride. A mixed ANOVA supported this interpretation, producing significant main effects of Dose, $F(2,21) = 81.99, p < .001$, and Session, $F(4,84) = 43.28, p < .001$, as well as a significant interaction, $F(8,84) = 12.62, p < .001$. Fisher's test indicated that rates of the alternative poke response were significantly suppressed in both raclopride groups relative to the saline control, but did not differ from one another. The significant interaction arose because Dose was significant at each session (all p values $< .01$) due to both groups treated with raclopride differing significantly from the 0 μg control group.

Thus, raclopride suppressed resurgence of the target lever and hastened extinction of the alternative nose poke across Phase III sessions at both doses tested. Slightly different patterns emerged between the two responses in the 50 μg group. Both responses fell to very low levels during the second Phase III session, but there was a subsequent increase in the target response, whereas the alternative poke remained suppressed almost completely.

Motivational versus motor impairment. Raclopride suppressed resurgence on the target lever during the first session of Phase III and throughout the remaining Phase III sessions; however, suppressed responding may be indicative of motivational or motor impairments. Although these effects are difficult to dissociate (see Grimm et al., 2011), previous studies have used a variety of measures to examine the effects of drugs on motivation to initiate responding, motivation to respond throughout the test session, and ability to respond (Alleweireldt et al., 2002; Grimm et al., 2011; Quick et al., 2011). A primary aim of some of these analyses is to determine whether responding under the influence of drug is similar to responding under extinction conditions. Animals are capable of responding during extinction, but presumably do not because there is no motivating consequence (i.e. reinforcement). Therefore, responding that resembles extinction-like responding is thought to result from motivational deficits and not motor impairment. Another aim of these analyses is to determine whether deficits are specific to responses associated with reward or if all behavior occurring within the session is suppressed. Whereas response reduction limited to behavior associated with reward is thought to reflect motivational impairment, nonspecific deficits are thought to result from motor impairment.

Analyses for the present experiment are somewhat unique in that the available responses in the chamber included not only a target and inactive lever, but also an alternative poke and other inactive pokes. Analyses of all available responses were needed because the target and alternative were associated with deliveries of

the same reinforcer (i.e., food pellets). Deficits in both responses would indicate a general change in motivation for food, whereas deficits in just the target would indicate that the drug did not have a general effect, but rather affected motivation to revert to a previously productive response.

Motivation to initiate responding. Alleweireldt and colleagues (2002) examined latency to the first target response as an index of motivation early in the session. The top panel Figure 3 shows average (\pm SEM) latencies to the first target and alternative responses in the first session of Phase III. Latency to the first target response was similar in the 0 and 50 μ g groups, but increased dramatically in the 100 μ g group (note the logarithmic y -axis). Table 2 contains individual subject data for these measures and shows that two subjects in particular (O7 and P7) influenced the mean and variation of the target latency in the 100 μ g group. Animals were faster to initiate the nose poke response regardless of group, and nose poke latencies showed less variation, but were dose-dependently increased by raclopride. A mixed ANOVA with Response as a within-subjects factor and Dose as a between-subjects factor indicated a nearly significant main effect of Response, $F(1,21) = 3.37$, $p = .081$, a significant main effect of Dose, $F(1,21) = 3.63$, $p = .044$, and a nearly significant interaction, $F(1,21) = 2.92$, $p = .076$. Fisher's test indicated that the 100 μ g group was significantly slower to initiate responding than the 0 and 50 μ g groups, which did not differ from one another. Although the interaction did not reach traditional levels of significance, simple main effects ANOVAs of Dose were conducted for each response to explore the nearly significant interaction. The effect

of dose was nearly significant for the target, $F(2,21) = 3.266, p = .058$, and did not reach significance for the alternative poke, $F(2,21) = 1.950, p = .167$. Thus, latencies for the target tended to be greater than for the alternative nose poke, but this is not surprising considering the nature of the experimental manipulation. That is, the poke was reinforced in the prior session, so it follows that subjects would initiate that

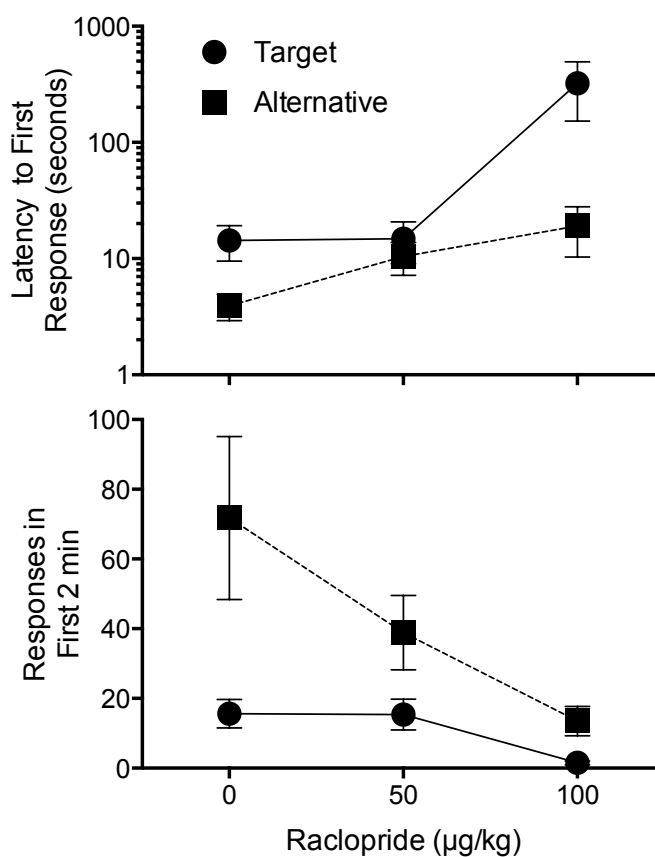


Figure 3. Effects of raclopride on mean (\pm SEM) latencies (top panel; note logarithmic y-axis) and number of responses emitted in the first 2 minutes (bottom panel) for the target and alternative responses the first Phase III session.

Table 2

Individual Subject Data for Motivational and Motor Measures During the First Phase III Session for Rats in Experiment 1

Dose	Subject	Total Responses			Average (SD) IRT		Latency		Resp. in First 2 Min.		Persistence		
		Target	Alt.	Inact. Other	Target	Alt.	Target	Alt.	Target	Alt.	Target	Alt.	
0 µg	O3	174	357	78	266	10.35 (13.36)	4.86 (8.24)	6.21	0.45	8	57	29.86	28.81
	O6	154	510	7	237	11.67 (11.85)	3.53 (5.64)	6.98	3.23	11	50	29.77	29.92
	P4	281	995	44	43	6.21 (12.97)	1.79 (7.64)	13.99	4.21	23	232	29.00	29.62
	P5	368	668	29	301	4.72 (8.48)	2.68 (4.56)	4.57	2.71	37	60	28.88	29.83
	R1	30	443	12	43	59.47 (48.17)	4.03 (8.91)	45.81	2.07	3	54	28.74	29.69
	R3	150	474	0	29	11.94 (16.11)	3.71 (10.59)	4.98	6.32	21	49	29.65	29.21
	R6	267	663	34	136	6.70 (7.40)	2.71 (3.94)	15.72	2.83	18	55	29.72	29.87
	R8	137	232	16	136	12.87 (16.47)	7.73 (11.94)	16.63	9.65	4	17	29.18	29.76
50 µg	O1	210	202	24	22	8.56 (21.71)	8.66 (24.77)	6.83	20.41	32	74	29.82	29.01
	O4	56	135	5	43	28.81 (40.94)	12.77 (40.36)	15.51	6.49	4	20	26.41	28.53
	O5	131	205	5	35	13.05 (16.37)	8.52 (17.61)	4.72	1.12	8	15	28.28	28.96
	O8	72	140	25	86	24.25 (53.30)	12.79 (26.54)	5.03	15.62	18	37	28.69	29.63
	P1	35	154	0	9	50.27 (62.05)	11.18 (25.75)	21.45	7.45	3	26	28.49	28.51
	P6	129	147	48	14	13.88 (23.75)	12.08 (36.48)	5.18	2.82	19	45	29.61	29.39
	R2	31	73	0	14	58.06 (104.09)	23.20 (38.15)	52.99	26.37	5	3	29.03	27.84
	R5	283	580	18	78	6.33 (10.78)	3.00 (8.59)	7.19	3.34	34	91	29.76	28.93
100 µg	O2	59	89	2	17	29.83 (33.09)	19.06 (39.69)	65.41	5.18	1	12	28.84	27.95
	O7	9	87	4	7	44.60 (70.96)	16.44 (65.97)	1023.61	8.04	0	36	5.95	23.57
	P2	1	16	8	6	-	96.84 (208.47)	123.65	8.14	0	7	0.00	24.21
	P3	18	10	7	11	94.15 (142.05)	100.71 (136.78)	35.89	7.22	3	3	26.68	15.11
	P7	1	47	1	21	-	23.34 (46.07)	1174.63	3.30	0	24	0.00	17.90
	P8	16	32	0	24	100.10 (167.88)	46.80 (76.23)	18.66	37.52	2	3	25.02	24.18
	R4	4	17	3	19	443.50 (450.46)	101.46 (197.60)	105.99	74.34	2	4	21.24	27.06
	R7	94	93	4	12	18.54 (21.88)	19.45 (37.98)	35.86	8.96	4	19	28.73	29.82

response before reverting to the target lever, which was reinforced more remotely at the end of Phase I. Furthermore, the 100 µg dose of raclopride significantly impacted latency to first response, but tended to have a larger impact on the target lever than on the alternative nose poke.

In a similar analysis, Grimm et al. (2011) examined the number of responses emitted during the first 2 minutes of an experimental test session to examine motivation to initiate responding. Average (\pm SEM) responses emitted during the first 2 minutes of the first Phase III session are shown in the bottom panel of Figure 3, and individual subject data for these measures are presented in Table 2. These results were highly similar to those of the latency data: More responses to the alternative poke occurred in the first 2 minutes of the session, and raclopride dose-dependently reduced early responses to the alternative nose poke, but appeared to impact the target lever only at the 100 µg dose. A mixed ANOVA yielded significant main effects of Response, $F(1,21) = 14.95, p = .001$, Dose, $F(1,21) = 4.54, p = .023$, and a nearly significant interaction, $F(1,21) = 2.80, p = .084$. Fisher's test indicated that the 100 µg group differed from the 0 µg group. Again, simple main effects ANOVAs were conducted for Dose at each response because the interaction approached significance. Raclopride had significant effects on the target lever presses, $F(2,21) = 5.43, p = .013$, and alternative pokes, $F(2,21) = 3.77, p = .040$. Fisher's test indicated that the 100 µg group differed from both the 0 and 50 µg groups in terms of target presses, but only the 0 and 100 µg groups differed in terms of early alternative pokes.

Not surprisingly results of analyses on responses made in the first 2 minutes largely paralleled those of the latencies. The 100 μg group emitted significantly fewer responses in the first 2 minutes of the session. Furthermore, the higher dose of raclopride had somewhat differential effects on the two responses in that target pressing was significantly different from the 0 and 50 μg groups, but alternative pokes were different from only the 0 μg group.

Motivation across the session. The impact of drugs on motivation throughout the session has also been examined to dissociate motivational and motor impairment. Alleweireldt and colleagues (2002) calculated a measure of persistence by subtracting the time of the first response from the time of the last response to determine the duration during which responses occurred throughout the session. Mean ($\pm\text{SEM}$) persistence scores for each group are shown for the target and alternative responses in Figure 4, and individual subject data are shown in Table 2. Persistence in the 0 and 50 μg groups was similar, but was lower in the 100 μg group. Furthermore, the target appeared to be less persistent than the alternative in 100 μg group, but as seen in Table 2, the group mean was dragged down by two persistence scores of 0 because only one target response was emitted. A mixed ANOVA indicated significant differences for Dose, $F(1,21) = 10.49, p = .001$, but not Response, $F(1,21) = 2.63, p = .120$, nor the interaction, $F(1,21) = 2.27, p = .128$. Fisher's test indicated that responding was less persistent in the 100 μg group than either the 0 or 50 μg groups. Thus, there was no statistical support for raclopride differentially affecting persistence of the two responses.

Quick and colleagues (2011) compared target response patterns throughout the last Phase II session and first Phase III session to determine whether drug administration produced responding similar to extinction, reasoning that extinction-like patterns imply motivational rather than motor deficits. Figure 5 shows the effects of raclopride on mean (\pm SEM) cumulative target presses across 2-minute bins of the last Phase II and first Phase III sessions. A mixed ANOVA with Phase and Bin as within-subjects factors and Dose as a between-subjects factor produced a significant 3-way interaction, $F(28, 294) = 6.86, p < .001$, along with all other 2-way interactions and main effects reaching significance. To explore this

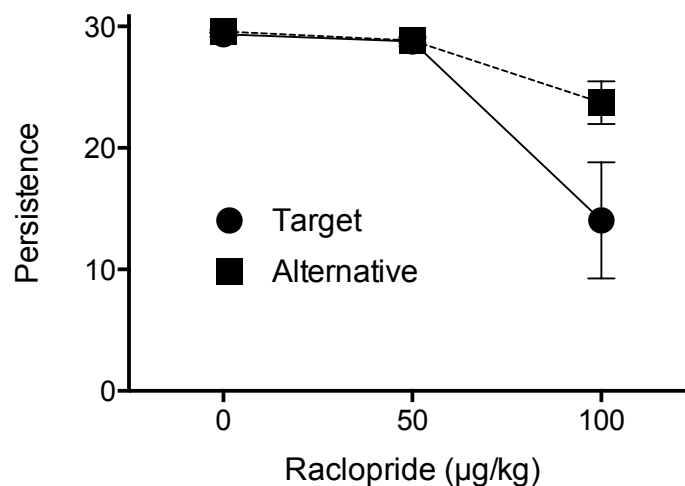


Figure 4. Effects of raclopride on mean (\pm SEM) persistence scores (time of last response minus time of first response) for the target and alternative responses in the first Phase III session.

significant interaction further, separate Dose \times Bin mixed ANOVAs were conducted for each Phase. Cumulative target presses increased similarly for all groups throughout the last session of Phase II as indicated by a significant main effect of Bin, $F(14,294) = 24.50, p < .001$, but a nonsignificant main effect Dose, $F(2,21) = .69, p = .512$, and nonsignificant interaction, $F(28,294) = 1.00, p = .473$. Accordingly, these data were collapsed across groups in Figure 5 (open diamonds). Raclopride dose-dependently decreased cumulative target response during Phase III as indicated by significant main effects of Dose, $F(2,21) = 8.03, p = .003$, Bin, $F(14,294) = 39.51, p < .001$, and a significant interaction, $F(28,294) = 7.65, p < .001$. Fisher's

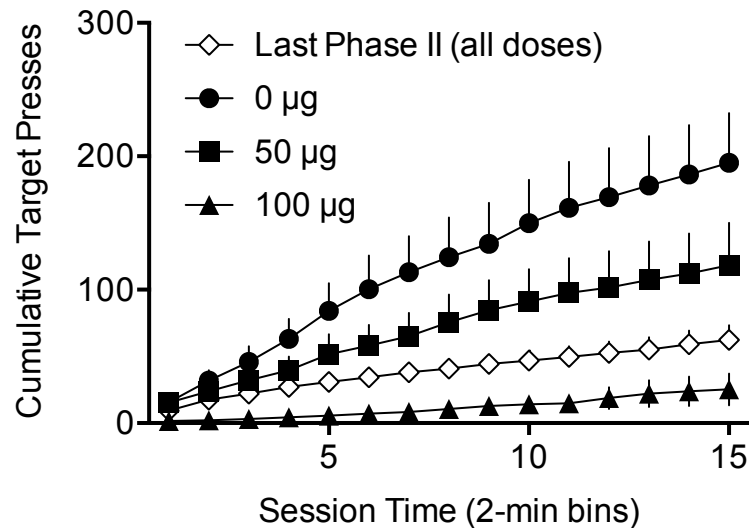


Figure 5. Effects of raclopride on mean (\pm SEM) cumulative target lever presses across 2-minute bins of the last Phase II and first Phase III sessions. Data from the last Phase II session did not differ significantly and were collapsed across treatment groups.

test indicated that the 100 µg group differed from the 0 and 50 µg groups, which did not differ from one another.

Additional Phase × Bin mixed ANOVAs were conducted for each group to determine whether raclopride produced extinction-like responding. Response patterns in the 0 µg group during Phase III were clearly different as indicated by a significant main effect of Phase, $F(1,7) = 15.83, p = .005$, Bin, $F(14,98) = 18.10, p < .001$, and a significant interaction, $F(14,98) = 23.00, p < .001$. Cumulative target presses in the 50 µg group did not differ markedly from extinction in that the main effect of Phase did not reach significance, $F(1,7) = 1.31, p = .289$, but the main effect of Bin, $F(14,98) = 19.79, p < .001$, and the interaction, $F(14,98) = 2.17, p = .014$, did reach significance. Cumulative target presses were significantly suppressed in the 100 µg group during Phase III as indicated by significant main effects of Phase, $F(1,7) = 11.29, p = .012$, and Bin, $F(14,98) = 12.04, p < .001$, but a nonsignificant interaction, $F(14,98) = 1.51, p = .120$.

In summary, the groups did not differ in terms of within-session response patterns during the last session of Phase II, but raclopride dose-dependently suppressed responding during the first Phase III session, and significant differences emerged between the 0 and 100 µg groups. Furthermore, cumulative target presses were significantly suppressed relative to extinction in Phase II for the 100 µg group.

Ability to respond. Alleweireldt and colleagues (2002) examined inter-response times (IRTs) of active responses to gauge whether drug administration impacted subjects' ability to respond. The top panel of Figure 6 shows average

(\pm SEM) IRTs for the target lever and alternative pokes during the first Phase III session. Table 2 displays mean (Standard Deviation; SD) IRTs for individual subjects, as well as the number of responses emitted. IRTs were generally lower for the alternative poke (i.e., responding was more frequent). The 50 μ g group looked similar to the 0 μ g group, but increases in IRTs for both responses were evident in the 100 μ g group. A mixed ANOVA with Response as a within-subjects factor and Dose as a between-

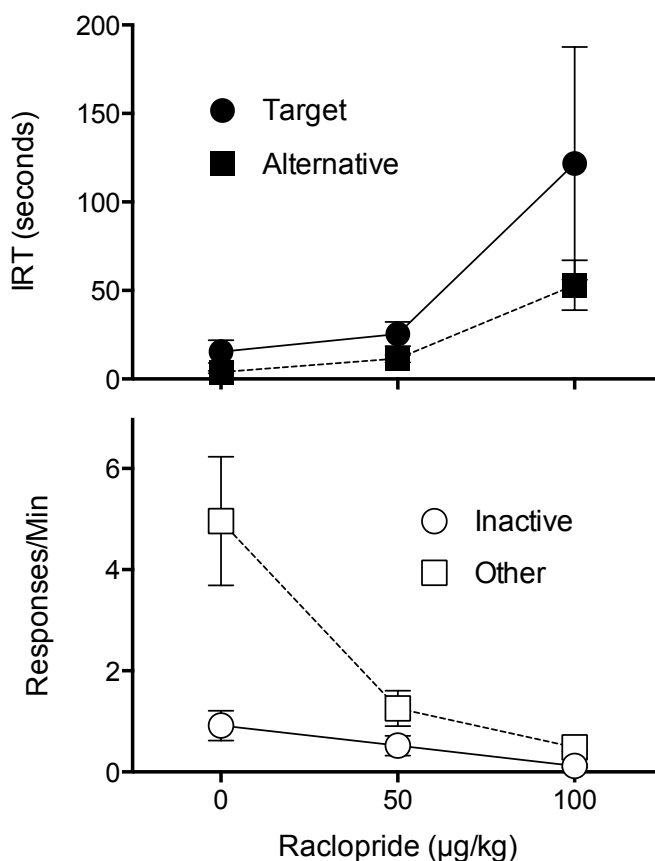


Figure 6. Effects of raclopride on mean (\pm SEM) IRTs for target lever and alternative poke (top panel) and on mean (\pm SEM) response rates for the inactive lever and other pokes (bottom panel).

subjects factor supported this interpretation, producing significant main effects of Response, $F(1,21) = 4.52, p = .047$, and Dose, $F(1,21) = 4.55, p = .024$, but a nonsignificant interaction, $F(1,21) = 1.50, p = .248$. Fisher's tests indicated that the 100 μg group differed from both 0 and 50 μg groups, which did not differ from one another.

Previous studies have also examined the effects of drugs on inactive response rates to dissociate motor from motivational effects because these rates tend to decrease when drugs produce general impairment (see Grimm et al., 2011; Quick et al., 2011). The bottom panel of Figure 6 shows response rates on the inactive lever, as well as all other nose pokes, in the first session of Phase III. Table 2 shows individual subject data. Within all groups more responding occurred to the other pokes than to the inactive lever. Raclopride dose-dependently reduced both responses, but the effect was more dramatic for the other nose pokes. Another mixed ANOVA with Response (Inactive versus Other) as a within-subjects factor and Dose as a between-subjects factor supported this interpretation, producing significant main effects of Response, $F(1,21) = 16.94, p < .001$, Dose, $F(1,21) = 10.48, p = .001$, and a significant interaction, $F(1,21) = 7.87, p = .003$. Simple main effects ANOVAs for Dose were then conducted for each response. Raclopride significantly impacted inactive lever pressing, $F(2,21) = 3.75, p = .041$, and other nose pokes, $F(2,21) = 9.81, p = .001$. Fisher's tests indicated only the 0 and 100 μg groups differed on inactive presses, whereas both groups treated with raclopride differed from the 0 μg group in terms of other pokes.

In summary, the 100 μg group differed significantly from the control group in terms of both IRTs of the target and alternative, as well as inactive and other response rates. These deficits suggest that the 100 $\mu\text{g}/\text{kg}$ dose of raclopride affected more than just motivation, and produced general disruption of motor behavior. Although rates of other nose pokes were impacted at the 50 μg dose, this group of animals did not show any other signs of motor impairment.

Discussion

There were no systematic differences in response or reinforcer rates among the groups during Phase I or Phase II. When reinforcement for the alternative nose poke response was discontinued during Phase III, administration of 50 and 100 $\mu\text{g}/\text{kg}$ raclopride reduced resurgence specific to the target lever. Raclopride also altered patterns of decline in target and alternative responding across Phase III sessions. Target responding was dose-dependently attenuated across sessions, and each pair of groups differed from one another. Patterns of the alternative poke were slightly different in that response rates in both groups treated with raclopride were almost nonexistent across Phase III sessions, and did not differ from one another, but differed from the 0 μg group.

Several additional measures were examined to rule out the possibility that raclopride reduced resurgence by interfering with the animals' ability to respond, and the results of these analyses are summarized in Table 3. First, motivation to

Table 3

Summary of Statistical Comparisons Between Control Group (0 μg) and Groups Treated with Raclopride and (50 and 100 μg) for Motivational and Motor Measures

Measure	Target		Alternative	
	50 μg	100 μg	50 μg	100 μg
First III	NS	*	*	*
Across III	*	*	*	*
Latency	NS	*	NS	*
First 2 min	NS	*	NS	*
Persistence	NS	*	NS	*
Cumulative	NS	*	-	-
IRT	NS	*	NS	*
Inactive/Other	NS	*	*	*

initiate responding was examined via two measures: latency to the first response and number of responses made in the first 2 minutes of the session. Across groups, animals were faster to initiate the alternative nose poke than the target lever press. However, the 100 μg group was slower than both 0 and 50 μg groups who did not differ, and the target was slightly more susceptible to slowing than the alternative. Not surprisingly given the latency data, more responding occurred to the alternative poke within the first 2 minutes of the session. The 100 μg group emitted fewer target presses than the 0 and 50 μg groups, but fewer alternative pokes than only the 0 μg group. Second, the persistence of each response was examined by calculating the duration of the session in which responding occurred (i.e., time of last response minus time of first response). Responding was less persistent in the 100 μg group

than the 0 and 50 μg groups, and there was visual evidence the target was less persistent, but the statistical analyses did not support this conclusion. Third, cumulative target patterns across the session were examined to determine whether responding was “extinction-like” (i.e., similar to Phase II). Within-session response patterns on the target lever were significantly different in the 100 μg group than the 0 and 50 μg groups. Furthermore, the 100 μg group displayed target response patterns during Phase III that were significantly suppressed relative to Phase II. Finally, the animals’ ability to respond was explored in two ways: examination of IRTs of the active and target responses, as well as rates of responses never associated with reinforcement to test for general impairment. IRTs were lower for the alternative poke (i.e., these responses occurred more frequently), and the 100 μg group responded less frequently than the 0 and 50 μg groups, which did not differ. More other pokes occurred than inactive lever presses in each of the groups. Fewer inactive presses occurred in the 100 μg group than the 0 μg group, but both raclopride groups emitted fewer other pokes than the 0 μg group.

Given that the group of rats that received the 100 $\mu\text{g}/\text{kg}$ dose of raclopride during Phase III showed significant deficits relative to the 0 μg group in every single measure just described, it appears that a general disruption of motor behavior may have contributed to the effects of the 100 $\mu\text{g}/\text{kg}$ dose on resurgence. While the 50 μg group showed little evidence of motor impairment in the measures that have been previously used to assess motor impairment, this group showed significant deficits

relative to the 0 μg group in the target and alternative responses across Phase III sessions. Thus, there is strong evidence for motor impairment at the 100 μg dose, but the evidence for the 50 μg group is more ambiguous, so attenuation of resurgence via motor impairment cannot be ruled out at either dose.

At least one previous study has reported motor impairment at the doses tested in the present study. Crombag and colleagues (2002) tested 50 and 100 $\mu\text{g}/\text{kg}$ raclopride on contextual renewal of cocaine seeking. They found that both doses attenuated renewal, but that these same doses also reduced active lever pressing in controls animals that were not exposed to the manipulation that induced drug seeking. These results are interesting in that they are consistent with Experiment 1 with respect to the 100, but not 50 $\mu\text{g}/\text{kg}$ dose. More specifically, there was little indication of motor impairment in the 50 μg group in the present experiment.

The results concerning motor impairment in the 100 μg group are also somewhat surprising in light of previous studies on reinstatement that have used the same or higher doses of raclopride and reported little or no evidence of motor impairment. For instance, Shaham and Stewart (1996) tested the effects of 250 and 500 $\mu\text{g}/\text{kg}$ raclopride on heroin- and shock-induced reinstatement, and both doses blocked shock-induced reinstatement, but left heroin-induced reinstatement intact. Cervo and colleagues (2003) tested the effects of 30, 100, and 300 $\mu\text{g}/\text{kg}$ raclopride on cue-induced reinstatement of cocaine seeking and found that 100 and 300 $\mu\text{g}/\text{kg}$

blocked reinstatement without affecting inactive lever presses. Tobin and colleagues (2009) tested 50 and 100 $\mu\text{g}/\text{kg}$ raclopride on food deprivation- and cue-induced reinstatement of heroin seeking. They found that raclopride did not block deprivation-induced reinstatement, but dose-dependently reduced cue-induced reinstatement. Raclopride did not affect inactive lever pressing in tests of either type of reinstatement. It is not entirely clear why so many studies have successfully used these high doses of raclopride in the absence of motor impairment, but it may be related to raclopride's effects on food- versus drug-maintained responding.

Previous studies have shown that raclopride may impact food-maintained behavior to a larger extent than drug-maintained behavior. Caine and Koob (1994) tested the effects of 50, 100, 200, and 400 $\mu\text{g}/\text{kg}$ raclopride on operant behavior in a multiple schedule in which periods of cocaine availability alternated with periods of food availability. Raclopride reduced responding for food to a greater extent than cocaine across doses, but these effects were only statistically significant at the two highest doses tested. Similarly, Weissenborn, Deroche, Koob, and Weiss (1996) tested the effects of 100, 200, and 400 $\mu\text{g}/\text{kg}$ raclopride on food- and cocaine-maintained behavior in a multiple schedule. They reported a downward trend in food-maintained behavior across doses, but these differences did not reach statistical significance. So, while there is some evidence of raclopride having differential effects on ongoing food- and drug-maintained behavior, it is not clear whether these results apply to relapse of extinguished behavior.

The results concerning the effects of raclopride on target lever pressing across Phase III sessions are not particularly surprising considering the well-documented effects of D₂ antagonists on various types of relapse. However, raclopride also significantly impacted extinction of the alternative nose poke across Phase III sessions. Furthermore, raclopride almost completely suppressed alternative pokes at both doses tested. To my knowledge, no studies have directly investigated the effects of dopamine D₂ antagonists on extinction of operant responding. However, Aberman, Ward, and Salamone (1998) explored the effects of raclopride on progressive-ratio performance, in which a response requirement is increased after each reinforcer delivery. Aberman and colleagues found that raclopride administered at doses comparable to those used in Experiment 1 suppressed progressive-ratio responding resulting in decreases in the highest ratio completed. If extinction is conceptualized as an infinitely long response requirement, then such results in progressive ratio schedules may have some bearing on the effects of D₂ antagonists during extinction, and the results concerning the alternative poke are not that surprising. However, the results of Aberman et al. do not speak to the speed at which raclopride eliminated the alternative poke in the present study.

In light of previous research it is interesting that in the present study impairments of motivation to initiate responding and motivation to persist in responding were aligned with one another. Alleweireldt and colleagues (2002) tested the effects of the dopamine D₁ antagonist SCH 23390 on cue-induced cocaine

seeking, and reported dissociable effects of deficits in initiation and persistence. That is, SCH 23390 did not affect motivation to initiate responding, but decreased persistence, which is typical of responding under extinction conditions. These differing results may be related to several differences between the two studies. First, Alleweireldt et al. examined action at the dopamine D₁ receptor, while the present experiment examined the role of D₂ receptors. There is evidence that dopamine D₂ receptor antagonism produces greater motor disruption of operant behavior than antagonism at D₁ receptors (see Fowler & Liou, 1998). Second, target responses produced a cue that accompanied cocaine deliveries in the past in the Alleweireldt et al. study, whereas the target had no programmed consequences in the present experiment. Finally, experimental sessions lasted 120 minutes in the Alleweireldt et al. study, whereas sessions were just 30 minutes long in the present experiment. Longer sessions may have produced deficits in persistence within the 50 µg group.

Some differences emerged between the effects of raclopride on the target versus alternative response. For instance, patterns of decline across Phase III sessions were markedly different: Raclopride nearly eliminated alternative pokes at both doses, whereas some target lever pressing occurred within the 50 µg group. Also, in measures of early responding (i.e., latency and responses in first 2 minutes), raclopride had clear effects on the alternative at both doses tested, whereas only the 100 µg/kg dose impacted the target. These results are interesting in the present experiment in that both responses produced the same reinforcer. Such effects may

be attributable to the rates at which the responses occurred prior to raclopride administration. That is, the target occurred at a much lower rather than the alternative poke. However, it may also be an issue of relapse versus extinction. That is, reappearance of an extinguished response versus elimination of a previously reinforced response.

Raclopride blocked resurgence in Experiment 1, but previous studies have shown that dopamine D₂ antagonists are ineffective in blocking stress-induced reinstatement (Capriles et al., 2003; Shaham & Stewart, 1996; Tobin et al., 2009). This provides some evidence that the food or drug seeking observed in resurgence experiments is not stress-induced. However, one of the primary aims of the present dissertation was to directly examine the role of receptors known to impact stress-induced reinstatement.

CHAPTER IV

EXPERIMENT 2: THE ROLE OF NORADRENERGIC α_2 RECEPTORS IN RESURGENCE**Purpose**

Both Podlesnik et al. (2006) and Quick et al. (2011) drew parallels between the reinforcer loss used to induce drug seeking within the resurgence procedure and situations such as job loss or divorce, which can produce increased drug taking and relapse within human populations (Falba et al., 2005; Gallo et al., 2001; San Jose et al., 2000; Temple et al., 1991). These and similar situations (e.g., death of a loved one, loss of a home, abandonment, etc.) are typically considered stressful circumstances (see Sinha, 2008); therefore, resurgence may be a form of stress-induced relapse.

Experiment 1 examined the role of dopamine D₂ receptors in resurgence, but antagonism of these receptors fails to attenuate stress-induced reinstatement (Capriles et al., 2003; Shaham & Stewart, 1996; Tobin et al., 2009). The purpose of Experiment 2 was to explore the role of receptors whose blockade reduces stress-induced relapse. The adrenergic α_2 receptor was chosen because α_2 agonists block stress-induced reinstatement of a variety of drugs of abuse (Erb et al., 2000; Shaham et al., 2000; Lê et al., 2005; Zislis et al., 2007).

As in Experiment 1, rats responded in a resurgence procedure in which a lever press produced food deliveries during Phase I, the lever press was placed on extinction while a nose poke produced food deliveries during Phase II, and finally

the nose poke was also placed on extinction while the lever remained on extinction during Phase III. Separate groups of animals were injected with vehicle or one of two doses of the α_2 receptor agonist clonidine prior to Phase III sessions.

Method

Subjects

An additional 24 experimentally naïve male Long-Evans rats were used in the present experiment. Details regarding housing, deprivation, and experimental handling were identical to those experienced by the animals in Experiment 1.

Apparatus

Four additional MED-Associates chambers were used for Experiment 2. These chambers were identical to those used in the previous experiment with the exception of details involving the levers, lever lights, and pellet receptacle. In these four chambers, an identically sized aperture (5 cm × 5 cm) sits between two fixed (i.e., non-retractable) levers; however, this aperture is divided in half vertically, and pellets are delivered on the right side. Above each lever to the left and right of the food aperture is a series of colored LEDs (red, yellow, green).

Drug

The α_2 adrenergic receptor agonist clonidine was used in the present study. Separate groups of rats ($n = 8$) were injected with 0 (vehicle), 20, or 40 $\mu\text{g}/\text{kg}$ of the

drug. These doses were chosen based on previous studies that demonstrated successful attenuation of shock-induced reinstatement without motor impairment (Erb et al., 2000; Shaham et al., 2000). All drug doses were prepared at an injection volume of 1 ml/kg. Clonidine or saline was administered via intraperitoneal injection 40 minutes prior to experimental sessions.

Procedure

Training. Magazine training occurred as described in Experiment 1 with pellets being delivered according to a VT 60-s schedule in a 30-minute session. The two additional FR 1 training sessions also occurred as described in Experiment 1.

Phases I, II, and III. Animals in Experiment 2 experienced identical experimental phases as outlined in the first experiment. Briefly, rats lever pressed for pellets according to a VI 45-s schedule for 20 sessions (Phase I), followed by extinction of the lever press in conjunction with reinforcement of the center nose poke according to a VI 10-s schedule for 10 sessions (Phase II), and finally both responses were placed on extinction for 5 sessions (Phase III). Prior to Phase III sessions, rats were injected with 0 (vehicle), 20, or 40 $\mu\text{g}/\text{kg}$ of the α_2 receptor agonist clonidine.

Results

Phase I

Animals acquired the target lever response without incident as in Experiment 1. The top portion of Table 4 shows response rates and reinforcer rates averaged over the last 3 sessions of Phase I. Again, rats were assigned to treatment groups so as to equate average target lever rates, and these groups were highly similar in terms of those rates, $F(2,21) = .01, p = .995$. Inactive lever rates tended to be higher than either the alternative or other pokes, but all of these responses occurred at rates much lower than the target. Food rates also did not differ across groups, $F(2,21) = .47, p = .633$, and were close to the programmed rate of reinforcement (i.e., 1.33 foods per minute).

Phase II

One rat belonging to the 0 μg group (N6) experienced an additional Phase II session because of a substantial decrease in response rates during session 10. Response rates nearly recovered to their prior levels in the following session, so N6 proceeded to Phase III and its data (with the exception of session 10) were included in all data analyses. As shown in the bottom portion of Table 4, response rates on the target lever were low with the extinction contingencies in effect, and did not differ across groups, $F(2,21) = .77, p = .477$. As in Experiment 1, rates of the alternative nose poke response at the end of Phase II were much higher than at the

Table 4

Mean (SEM) Response and Food Rates Averaged over the Final Three Sessions of Phase I and Phase II for Rats in Experiment 2

	Group		
	0 µg	20 µg	40 µg
Phase I			
Target	32.77 (8.26)	33.07 (9.19)	33.93 (7.55)
Alt	0.12 (0.03)	0.08 (0.03)	0.12 (0.04)
Inactive	0.99 (0.42)	2.75 (1.67)	1.28 (0.44)
Other	0.73 (0.20)	0.44 (0.18)	0.57 (0.21)
Foods	1.19 (0.03)	1.22 (0.02)	1.19 (0.03)
Phase II			
Target	2.74 (0.76)	2.22 (0.29)	3.87 (1.45)
Alt	48.54 (11.42)	52.81 (11.98)	36.75 (5.40)
Inactive	0.32 (0.15)	0.69 (0.34)	1.91 (1.38)
Other	4.98 (1.51)	3.79 (2.38)	7.44 (2.41)
Foods	4.62 (0.40)	4.79 (0.21)	4.66 (0.17)

end of Phase I, and although rates in the 40 µg group were lower than the other two groups, these differences did not reach statistical significance, $F(2,21) = .69, p = .515$. As expected, food rates were also higher than in Phase I, and were similar across groups, $F(2,21) = .10, p = .904$. As in Experiment 1, obtained rates of reinforcement fell short of the programmed rates (i.e., 6 foods per minute). With the exception of the 40 µg group, inactive lever presses decreased from Phase I to Phase

II; however, rates of responding in the other nose pokes increased for all groups as they did in Experiment 1.

Phase III

Resurgence in first Phase III session. As in Experiment 1, responding on the target lever between Phase II and III was examined in the context of the inactive lever and other pokes to ensure that increased responding was specific to a response that previously produced food deliveries. Response rates on the target lever in the last session of Phase II and the first of Phase III are shown in the top panel of Figure 7. As in Experiment 1, responding was generally higher during Phase III, and varied according to clonidine treatment. A mixed ANOVA with Dose as a between-subjects factor and Phase as a repeated factor supported this account, indicating a significant main effect of Phase, $F(1,21) = 20.39, p < .001$, and significant interaction, $F(2,21) = 5.55, p = .012$, but the main effect of Dose failed to reach significance, $F(2,21) = 1.43, p = .261$. Follow-up paired t -tests comparing Phase II significant resurgence in the 0 μg , $t(7) = -4.12, p = .004$, and 20 μg , $t(7) = -2.43, p = .045$, but not 40 μg group, $t(7) = -.44, p = .672$. Thus, clonidine attenuated resurgence of the target lever at both doses tested, but only significantly at the highest dose tested, 40 μg .

The middle panel of Figure 7 shows response rates on the inactive lever in the last session of Phase II and the first of Phase III. Inactive lever pressing was lower in the 0 and 20 μg groups than in the 40 μg group across phases. The 0 and 20

μg also showed negligible increases in inactive lever pressing, whereas the 40 μg group showed a slight decrease. However, none of these differences were significant: The mixed ANOVA produced nonsignificant main effects of Phase,

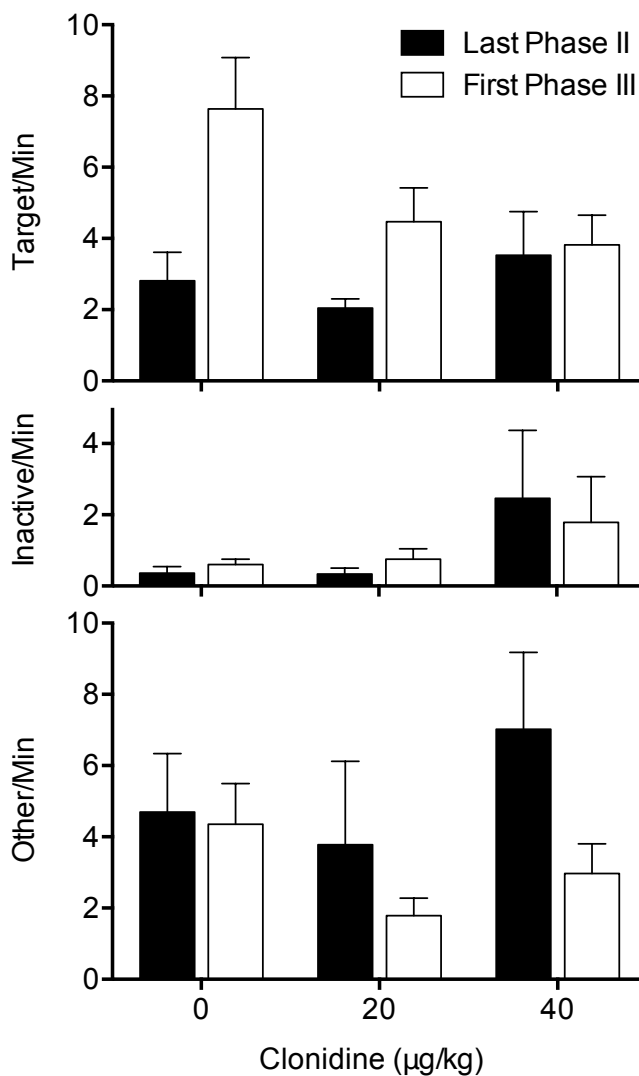


Figure 7. Effects of clonidine on mean (\pm SEM) response rates on the target lever (top panel), inactive lever (middle panel), and other pokes (bottom panel) within the last session of Phase II and first session of Phase III.

$F(1,21) = .001, p = .970$, and Dose, $F(2,21) = 1.00, p = .383$, as well as a nonsignificant interaction, $F(2,21) = 2.15, p = .142$. The bottom panel of Figure 7 shows response rates on the other nose pokes. Like the inactive lever presses, these pokes tended to occur less frequently in the 0 and 20 μg groups as compared to the 40 μg group. Both groups treated with clonidine showed decreased levels of other poking in Phase III, whereas other pokes in the 0 μg group were roughly the same. Significantly fewer other pokes occurred in Phase III as evidence by the mixed ANOVA producing a significant effect of Phase, $F(1,21) = 6.32, p = .020$. No other differences were significantly different, as indicated by the main effect of Dose, $F(2,21) = .69, p = .514$, and the interaction, $F(2,21) = 1.61, p = .223$, failing to reach significance.

Resurgence specific to the target lever occurred in the 0 and 20 μg groups, but was blocked by 40 μg of clonidine. Although responses to the other nose pokes decreased in Phase III as in Experiment 1, it is more difficult to say that this decrease was a product of the experimental contingencies and not the drug effects, because no such decrease was observed in the 0 μg group.

Across Phase III sessions. The top panel of Figure 8 shows target lever rates across Phase III sessions. A mixed ANOVA with Dose as a between-subjects factor and Session as a repeated measure showed that response rates decreased across sessions as indicated by a significant main effect of Session, $F(4,84) = 19.26, p < .001$, and were impacted by clonidine as indicated by a significant main effect of Dose, $F(2,21) = 4.04, p = .033$. Fisher's test showed that responding was significantly

lower in the 40 μg group than the 0 μg group, but no other comparisons reached significance. Rate of decline was similar across groups as indicated by a nonsignificant interaction, $F(8,84) = 1.506, p = .167$. Thus, 40 μg clonidine reduced target responding across Phase III sessions, but did not appear to hasten the rate of decline across those sessions.

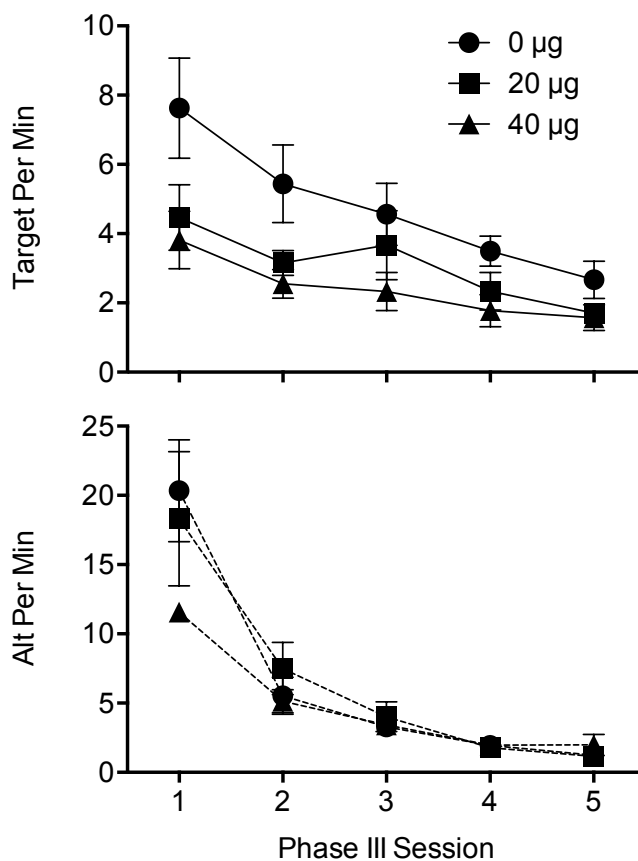


Figure 8. Effects of clonidine on mean (\pm SEM) response rates for the target lever (top panel) and alternative poke (bottom panel) across Phase III sessions.

The bottom panel of Figure 8 shows response rates on the alternative poke across Phase III sessions. Although responding in the 40 μg group was somewhat suppressed in the first session, rates of the alternative poke decreased similarly across sessions in all groups. A mixed ANOVA supported this interpretation yielding a significant main effect of Session, $F(4,84) = 51.43, p < .001$, but not Dose, $F(2,21) = .76, p = .478$, nor interaction, $F(8,84) = 1.97, p = .060$. Although the interaction almost reached statistical significance, the effect of Dose did not reach significance within any of the Phase III sessions (all p values $> .20$) indicating that clonidine did not significantly impact extinction of the alternative poke response across Phase III sessions. Thus, clonidine reduced activity at the target lever across Phase III sessions while leaving activity at the alternative poke relatively intact.

Motivational versus motor impairment. As in Experiment 1, a number of measures were analyzed to determine whether clonidine suppressed resurgence via alteration of motivation or by impairing motor performance. These measures examined motivation to initiate responding, motivation to respond throughout the session, and ability to respond.

Motivation to initiate responding. The top panel of Figure 9 shows the effects of clonidine on mean ($\pm\text{SEM}$) latencies to the first target and alternative responses in the first Phase III session, and individual subject data are displayed in Table 5. Subjects were quicker to initiate responding on the alternative response, but clonidine had no systematic effects on the target or alternative. This was supported by a mixed ANOVA with Response as a within-subjects factor and Dose as

a between-subjects factor that yielded a significant main effect of Response, $F(1,21) = 7.74$, $p = .011$, but neither Dose, $F(1,21) = .72$, $p = .499$, nor interaction, $F(1,21) = .64$, $p = .540$.

The bottom panel of Figure 9 shows the effects of clonidine on target and alternative responses in the first 2 minutes of the first Phase III session, and individual subject data for these measures are also shown in Table 5. As in

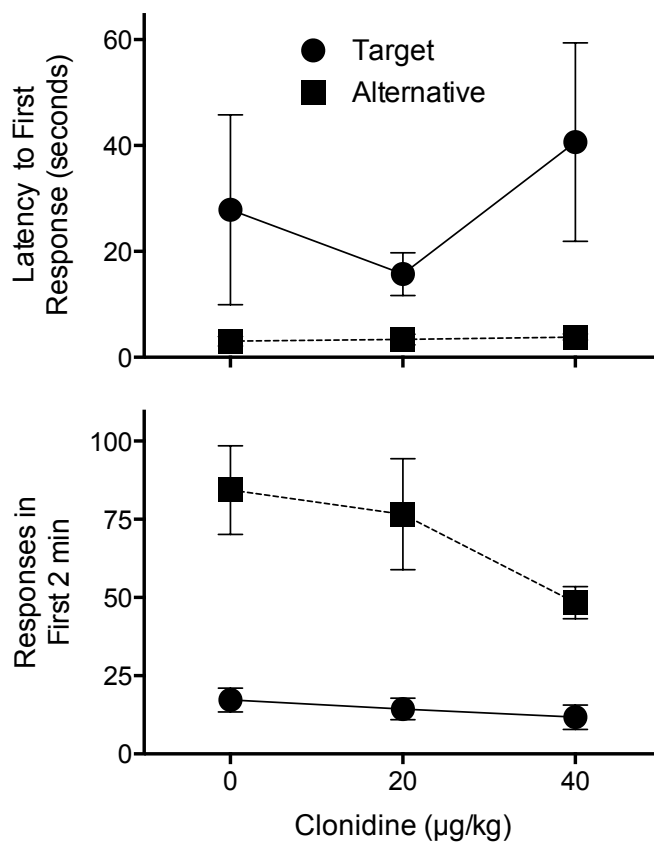


Figure 9. Effects of clonidine on mean (\pm SEM) latencies (top panel) and number of responses emitted in the first 2 minutes (bottom panel) for the target and alternative responses the first Phase III session.

Table 5

Individual Subject Data for Motivational and Motor Measures During the First Phase III Session for Rats in Experiment 2

Dose	Subject	Total Responses			Average (SD) IRT		Latency		Resp. in First 2 Min.		Persistence		
		Target	Alt.	Inact. Other	Target	Alt.	Target	Alt.	Target	Alt.	Target	Alt.	
0 µg	B3	388	928	32	112	4.61 (9.26)	1.93 (4.49)	16.15	1.79	26	89	29.73	29.87
	B7	141	869	22	149	12.76 (13.11)	2.06 (4.74)	6.28	4.17	13	95	29.77	29.77
	G3	181	347	36	157	9.91 (17.16)	5.04 (7.57)	4.32	1.79	18	56	29.73	29.04
	G6	285	651	17	341	6.28 (7.38)	2.75 (3.86)	12.94	7.29	26	83	29.71	29.84
	G8	261	615	2	90	6.79 (10.58)	2.55 (11.77)	9.82	0.77	14	131	29.44	26.14
	N1	38	63	11	16	47.25 (64.83)	28.78 (70.36)	16.47	6.02	8	18	29.14	29.74
20 µg	N2	153	454	0	123	10.84 (18.23)	3.76 (8.33)	152.77	1.40	0	62	27.45	28.39
	N6	383	953	24	57	4.67 (10.99)	1.88 (4.59)	4.03	1.07	33	141	29.75	29.88
	B4	50	551	2	8	34.86 (56.05)	3.26 (5.32)	21.79	5.99	6	59	28.47	29.90
	B6	105	414	13	141	17.06 (15.27)	4.34 (5.35)	17.57	3.68	8	59	29.58	29.88
	B8	111	1456	1	79	15.78 (17.67)	1.23 (2.70)	21.09	2.36	7	158	28.94	29.78
	G1	268	694	42	17	6.58 (20.27)	2.60 (10.30)	35.32	0.04	35	152	29.30	29.99
40 µg	G4	86	214	6	38	20.49 (28.36)	8.30 (16.71)	6.12	0.62	18	43	29.03	29.45
	G5	246	218	4	56	7.15 (13.21)	8.18 (12.15)	18.91	4.62	15	30	29.18	29.60
	N3	70	609	62	55	25.24 (30.08)	2.95 (7.28)	0.80	8.11	8	73	29.03	29.86
	N5	136	238	51	35	13.30 (15.99)	7.49 (11.33)	4.17	1.46	18	39	29.92	29.58
	B1	169	362	322	101	5.54 (14.40)	4.98 (8.18)	38.00	2.35	4	33	29.23	29.94
	B2	45	365	9	7	39.32 (44.25)	4.87 (12.63)	11.81	3.99	5	62	28.83	29.56
40 µg	B5	184	351	27	24	9.66 (14.62)	5.08 (12.71)	3.93	6.50	20	60	29.48	29.65
	G2	52	328	1	209	31.82 (62.63)	5.48 (10.39)	157.06	3.60	0	38	27.05	29.88
	G7	217	430	26	140	8.19 (16.15)	4.18 (12.63)	21.05	5.54	32	70	29.50	29.89
	N4	75	330	21	136	20.31 (46.72)	4.94 (17.41)	78.06	2.20	4	51	25.05	27.09
	N7	134	303	8	21	12.78 (20.46)	5.90 (14.24)	8.14	4.25	19	41	28.34	29.71
	N8	40	307	15	74	44.38 (76.92)	5.65 (10.44)	7.28	2.21	10	32	28.85	28.83

Experiment 1, more responding occurred on the alternative poke than the target lever. Clonidine subtly, dose-dependently reduced initial responding on the target lever, but seemed to have much more pronounced effects on the alternative poke. This interpretation was not supported statistically in that the mixed ANOVA only indicated a significant effect of Response, $F(1,21) = 59.18, p < .001$, but not Dose, $F(1,21) = 1.99, p = .162$, nor interaction, $F(1,21) = 1.73, p = .202$. Thus, although there appeared to be some effect on early alternative responses, especially on the number of alternative pokes within the first 2 minutes, clonidine did not produce any statistically different effects.

Motivation across the session. As in Experiment 1, persistence scores for the target and alternative responses were calculated by subtracting the time of the first response from the time of the last response. The effects of clonidine on mean (\pm SEM) persistence scores are displayed in Figure 10. Individual subject data are shown in Table 5. Persistence of the alternative response tended to be greater than the target for both groups treated with clonidine. This was supported by a mixed ANOVA with Response as a within-subjects factor and Dose as a between-subjects factor that yielded a significant effect of Response, $F(1,21) = 4.87, p = .039$, but not Dose, $F(1,21) = 1.24, p = .311$, and a nearly significant interaction, $F(1,21) = 3.42, p = .052$. The marginally significant interaction was analyzed further. First, the effect of Dose was examined for each response, but did not reach significance for the Target, $F(2,21) = 2.42, p = .113$, nor Alternative, $F(2,21) = 1.04, p = .370$. Accordingly, follow-up paired t -tests comparing the two responses were conducted for each dose, and

these indicated that the responses did not differ in the 0 μg group, $t(7) = .55$, $p = .599$, but did in the 20 μg , $t(7) = -3.17$, $p = .016$, and 40 μg group, $t(7) = -2.94$, $p = .022$. Thus, although responding occurred throughout most of the session across the groups, clonidine made the target response less persistent at both doses tested.

Cumulative target lever presses within the last Phase II and first Phase III sessions were also compared to examine whether response patterns were like those observed under extinction conditions (see Quick et al., 2011), and these data are shown in Figure 11. A Phase \times Dose \times Bin mixed ANOVA yielded a significant 3-way interaction, $F(28,294) = 4.93$, $p < .001$, along with all other 2-way interactions and main effects reaching significance, with the exception of Dose, $F(2,21) = 1.12$, $p =$

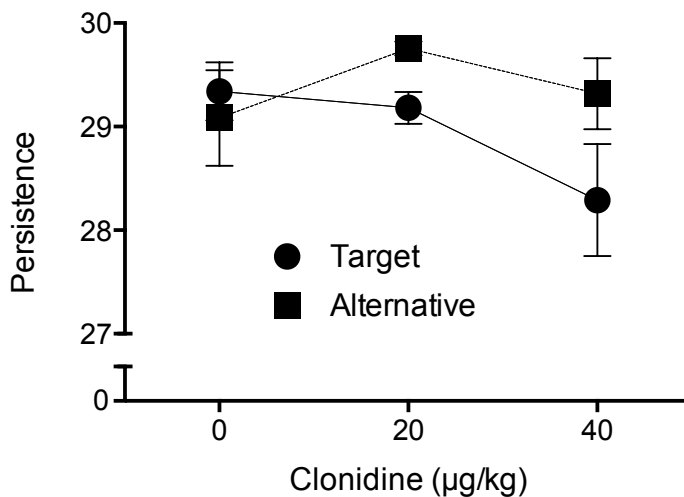


Figure 10. Effects of clonidine on mean (\pm SEM) persistence scores (time of last response minus time of first response) for the target and alternative responses in the first Phase III session. Note the break in the y-axis.

.345. The significant 3-way interaction was first followed up with separate Dose \times Bin mixed ANOVAs for Phase II and III. Responding increased similarly throughout the last Phase II sessions for all groups as indicated by a significant main effect of Bin, $F(14,294) = 29.96, p < .001$, but nonsignificant main effect of Dose, $F(2,21) = .85, p = .441$, and a nonsignificant interaction, $F(28,294) = .72, p = .848$. Thus, data from the last sessions of Phase II are collapsed across groups in Figure 6 (open diamonds). During Phase III, clonidine reduced cumulative target presses to similar levels below that of the 0 μg group. However, analysis of cumulative target presses during Phase III revealed a significant main effect of Bin, $F(14,294) = 63.12, p < .001$, and interaction, $F(28, 294) = 3.51, p < .001$, but only a marginally significant main

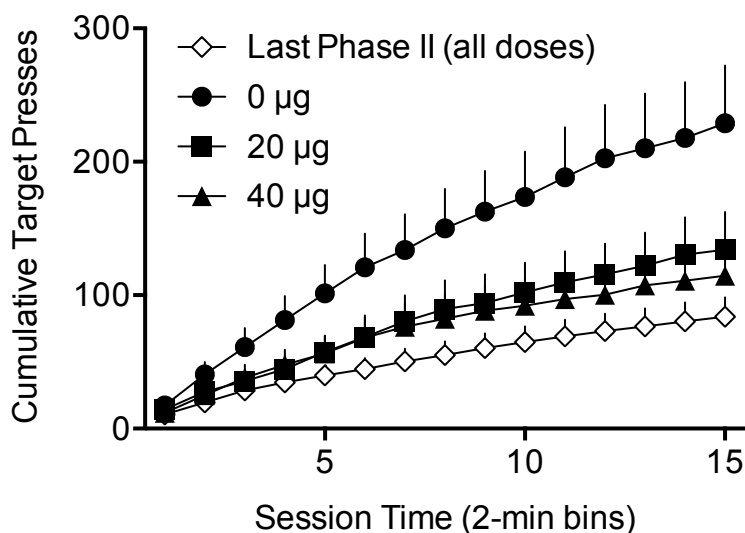


Figure 11. Effects of clonidine on mean (\pm SEM) cumulative target lever presses across 2-minute bins of the last Phase II and first Phase III sessions. Data from the last Phase II session did not differ significantly and were collapsed across treatment groups.

effect of Dose, $F(1,21) = 2.85, p = .080$.

Unlike Experiment 1, output on the target lever was greater during Phase III than for Phase II in each of the group. Additional Phase \times Bin mixed ANOVAs were conducted for each dose to compare within-session response patterns between Phases II and III. Patterns of cumulative target presses were significantly different in the 0 μg [Phase, $F(1,7) = 19.17, p = .003$; Bin, $F(14,98) = 24.50, p < .001$; Interaction, $F(14,98) = 14.91, p < .001$], and 20 μg groups [Phase, $F(1,7) = 5.51, p = .051$; Bin, $F(14,98) = 32.85, p < .001$; Interaction, $F(14,98) = 6.40, p < .001$], but not in the 40 μg group [Phase, $F(1,7) = .68, p = .694$; Bin, $F(14,98) = 13.18, p < .001$; Interaction, $F(14,98) = .87, p = .594$]. Thus, there was no evidence in the cumulative target data that clonidine decreased behavior to levels lower than observed under extinction conditions.

Ability to respond. Again, IRTs for the target and alternative were examined to determine whether ability to respond was impaired. The top panel of Figure 12 shows IRTs for the target and alternative responses. Table 5 shows individual subject mean (SD) IRTs, as well as the number of responses on which those averages are based. Responses to the alternative tended to occur in quick succession and were largely unaffected by clonidine. IRTs for the target response were longer than the alternative, and were dose-dependently increased by clonidine. A mixed ANOVA (Response \times Dose) produced a significant main effect of Response, $F(1,21) = 28.57, p < .001$, but neither Dose, $F(1,21) = .41, p = .669$, nor interaction, $F(1,21) = 1.55, p = .235$. Therefore, although there was some visual differentiation in the effects of

clonidine on the two responses, these differences were not statistically significant. Inactive and other nose pokes were also examined to rule out general disruption of behavior. The bottom panel of Figure 12 shows response rates for the inactive lever and other nose pokes during the first Phase III session, and individual subject data are shown in Table 5. Inactive lever rates tended to be lower than rates of other

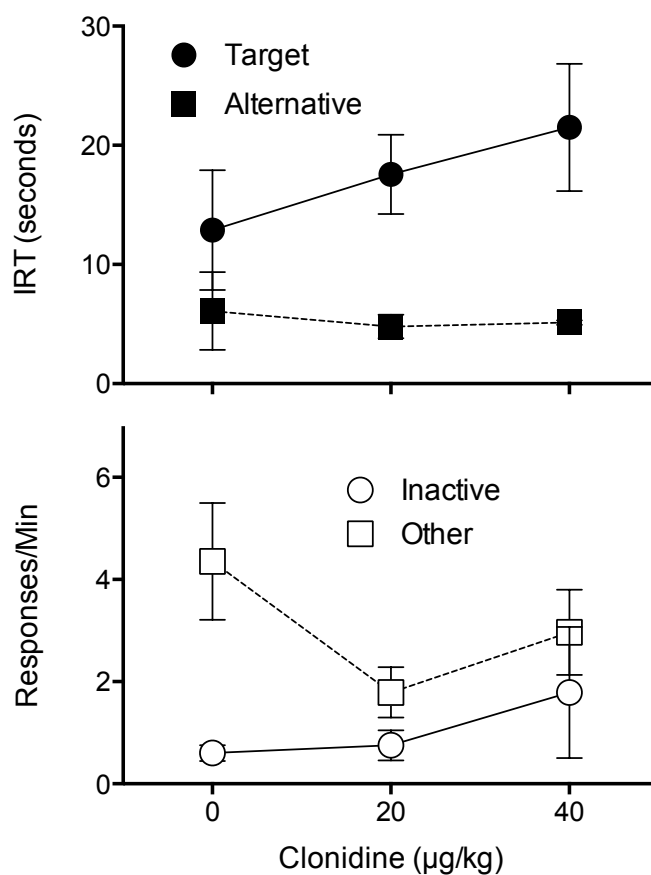


Figure 12. Effects of clonidine on mean (\pm SEM) IRTs for target lever and alternative poke (top panel) and on mean (\pm SEM) response rates for the inactive lever and other pokes (bottom panel).

pokes, however clonidine did not appear to produce any systematic changes in either response. This interpretation was supported by a significant main effect of Response, $F(1,21) = 9.15, p < .001$, but neither Dose, $F(1,21) = 1.31, p = .292$, nor interaction, $F(1,21) = 1.80, p = .190$.

As in Experiment 1, alternative nose pokes occurred more frequently than target lever presses, and response rates to the other nose pokes were higher than to the inactive lever. Unlike Experiment 1, analyses of IRTs and rates of inactive lever presses and other nose pokes indicated the clonidine did not impact ability to respond or produce any general disruption to behavior in the first Phase III session.

Discussion

As in Experiment 1, the groups were very similar in terms of response and reinforcer rates across Phases I and II. However, different patterns emerged during Phase III. Resurgence specific to the target lever was dose-dependently reduced by clonidine, but to levels that were not statistically different from Phase II only at the 40 $\mu\text{g}/\text{kg}$ dose. There was little change in inactive lever pressing from the end of Phase II to the beginning of Phase III; however, clonidine reduced rates of other pokes at both doses tested. Clonidine also dose-dependently reduced target lever pressing across Phase III sessions, but did not impact the rate of decline. Responses to the alternative poke showed a different pattern across Phase III sessions in that clonidine had no impact on the rate of extinction.

Unlike Experiment 1, attenuation of resurgence occurred largely in the absence of any evidence of motor impairment (see Table 6). Analyses of responding early in the session showed that rats were faster to initiate contact with the alternative nose poke than the target lever, and also made more alternative nose pokes than target lever presses in the first 2 minutes of the session. However, clonidine did not produce any statistically significant changes in either of these measures. Analyses of binned cumulative target presses showed that clonidine had little effect on within-session patterns of responding, and more (0 μ g) or equal (20 and 40 μ g) target responding occurred in the first Phase III session as compared to the last Phase II session. Although there was some visual evidence that clonidine dose-dependently increased IRTs for the target, the statistical evidence did not support that conclusion. Similar to Experiment 1, responding was less frequent on the inactive lever than in the other nose pokes; however, clonidine did not systematically affect these rates.

The one measure in which clonidine produced a response deficit was persistence of the target lever press. That is, the duration of the session during which target lever pressing occurred was slightly, but significantly shorter than it was for the alternative poke in both of the groups treated with clonidine. Considering that the groups did not vary with respect to latency to initiate target responding, this result suggests that these animals stopped responding at the target lever somewhat faster than they did the alternative. As noted earlier, deficits in persistence in the absence of any deficits in measures of motivation to initiate

Table 6

Summary of Statistical Comparisons Between Control Group (0 μg) and Groups Treated with Clonidine and (20 and 40 μg) for Motivational and Motor Measures

Measure	Target		Alternative	
	20 μg	40 μg	20 μg	40 μg
First III	NS	NS	NS	NS
Across III	NS	*	NS	NS
Latency	NS	NS	NS	NS
First 2 min	NS	NS	NS	NS
Persistence	NS	NS	NS	NS
Cumulative	NS	NS	-	-
IRT	NS	NS	NS	NS
Inactive/Other	NS	NS	NS	NS

responding are indicative of extinction-like behavior and are not likely attributable to motor impairment (see Alleweireldt et al., 2002).

The doses of clonidine examined in Experiment 2 were chosen based on previous studies that reported reduction of stress-induced reinstatement in the absence of motor impairment. Erb and colleagues (2000) tested 20 and 40 $\mu\text{g}/\text{kg}$ clonidine and found that while these doses blocked stress-induced reinstatement of cocaine seeking, these same doses did not impact saline or cocaine-primed reinstatement. Shaham and colleagues (2000) examined the effects of 0, 10, 20, and 40 $\mu\text{g}/\text{kg}$ clonidine on various durations of shock-induced reinstatement, and found that all doses tested blocked reinstatement across all shock durations. Importantly, clonidine did not impact active or inactive lever pressing in a control condition

when rats were not exposed to shock. However, at least one study has reported results that suggest motor impairment at the doses tested here. Smith and Aston-Jones (2011) tested administration of 5, 10, and 20 $\mu\text{g}/\text{kg}$ clonidine on cue-induced reinstatement of cocaine seeking, and reported that only the 20 μg dose effectively suppressed reinstatement to levels statistically indistinguishable from extinction, but that both the 10 and 20 $\mu\text{g}/\text{kg}$ doses significantly suppressed inactive lever presses.

In the present study clonidine did not impact extinction of the alternative response. Previous studies have examined the effects of α_2 agonists on extinction of operant behavior, but outcomes seem to be affected to some degree by whether cues accompanied reinforcer delivery during baseline and whether those cues were present during extinction. For instance, Highfield et al. (2001) reported that lofexidine injections have no effect on extinction of speedball (i.e., cocaine + heroin) self-administration if cues that accompanied drug deliveries were present during extinction, but reduced extinction responding when the cues were withheld. Consistent with these results, Smith and Aston-Jones (2011) demonstrated that 20 $\mu\text{g}/\text{kg}$ clonidine reduced cocaine seeking during the first extinction session when no previously cocaine-paired cues were present; however, this dose of clonidine also significantly reduced inactive lever pressing. Contrary to these results, Buffalari et al. (2012) compared extinction of a previously cocaine-maintained response between groups that received saline or guanfacine prior to extinction sessions in

which drug-paired cues were withheld, and they reported no differences between the two groups.

Within the present experiments the pellet receptacle was lit during reinforcer deliveries, but no such cue accompanied responses made under extinction conditions. Therefore, the results of Experiment 2 seem most consistent with the findings of Smith and Aston-Jones (2011) and Buffalari et al. (2012). That is, rates of decline of the alternative poke did not vary among the groups, but alternative rates were lower in 40 μ g group during the first Phase III session (see bottom panel of Figure 8), although not significantly lower, $F(2,21) = 1.70$, $p = .207$.

In summary, the results of Experiment 2 provide evidence of the involvement of α_2 receptors in resurgence. As noted, earlier, α_2 receptors are involved in other types of reinstatement, so Experiment 2 provides further evidence of common neuropharmacology among the widely used animal models of relapse. Data concerning effects of clonidine on the alternative response are especially interesting in light of the results of Experiment 1. More specifically, raclopride virtually eliminated the alternative poke early on in Phase III while clonidine had little to no effect.

CHAPTER V

GENERAL DISCUSSION

Summary

In Experiment 1, treatment with 50 and 100 $\mu\text{g}/\text{kg}$ of the D_2 antagonist raclopride significantly reduced resurgence of food maintained behavior. However, subsequent analyses of measures previously used to dissociate motor and motivational impairment (see Alleweireldt et al., 2002; Grimm et al., 2011; Quick et al., 2011) indicated that the reduction at the higher dose might have been due to motor impairment. Although the lower dose of raclopride showed little indication of motor impairment in these analyses, raclopride hastened the rate of decline for both the target and alternative responses across Phase III sessions at both doses tested. Thus, it is difficult to say whether motor impair also played a role in attenuation at the 50 μg dose. Raclopride appeared to have a larger impact on the alternative poke, nearly eliminating at both doses of raclopride tested, whereas the same suppressive effect was only observed on the target repose at the 100 $\mu\text{g}/\text{kg}$ dose. Furthermore, there was evidence that raclopride differentially affected motivation to initiate responding in that the drug dose-dependently reduced motivation for the alternative, yet only seemed to impact the target at the 100 $\mu\text{g}/\text{kg}$ dose.

In Experiment 2, administration of 20 and 40 $\mu\text{g}/\text{kg}$ of α_2 -adrenergic agonist reduced resurgence; however, only the highest dose tested effectively reduced resurgence to levels no different than extinction. Subsequent analyses indicated that

there was no evidence of motor impairment at either dose tested. Unlike Experiment 1, clonidine reduced responding on the target lever across Phase III sessions without impacting the rate of extinction of the alternative poke. Thus, Experiment 2 provided strong evidence that clonidine reduced resurgence via motivational rather than motor impairment.

Implications

Resurgence of Drug Seeking

The present studies examined resurgence of a previously food-maintained response as a preliminary investigation into whether D_2 and α_2 receptors play a role in resurgence. However, the majority of the literature that has informed the present design has examined relapse to drug seeking. Although few studies have examined the effects of these drugs on relapse to food seeking, some discrepancies have been noted between the effects of these drugs on drug and food seeking. For instance, administration of D_2 antagonists has previously potentiated (Ball et al., 2011) or had no effect (Gál & Gyertyán, 2006) on cue-induced reinstatement of food seeking, whereas these drugs typically reduce cue-induced drug seeking (Gál & Gyertyán, 2006; Liu et al., 2010; Tobin et al., 2009). Also, adrenergic α_2 agonists do not reduce yohimbine-induced reinstatement of food seeking (Lê et al., 2011; Nair et al., 2009), whereas these drugs readily block yohimbine-induced drug seeking (Lê et al., 2009; Lee et al., 2003). Therefore, future studies will need to assess the effects of these

drugs on resurgence of drug seeking, in which the target response is associated with drug deliveries and the alternative is associated with a nondrug reinforcer (e.g., Podlesnik et al., 2006; Quick et al., 2011).

The fact that both the target and alternative response produced the same nondrug reinforcer in the present experiments may also limit the treatment implications of the findings. Dissociation of effects on drug versus food seeking is important for behavioral interventions that attempt to curb drug taking. However, not all behavioral interventions aim to reduce drug-maintained behavior. For instance, many behavioral interventions attempt to replace maladaptive behaviors with more functional ones that result in the same consequence.

Treatment

Raclopride and clonidine both reduced resurgence of the target lever press, but raclopride also suppressed the alternative response, while clonidine had minimal impact. In DRA-based treatments for which results of resurgence research are most applicable, the alternative response is typically a functional one that would be undesirable to reduce. Based on the present results, clonidine appears to be a more viable option as a pharmacological treatment to supplement behavioral interventions. Interestingly, previous studies have examined the effects of both D_2 antagonists and α_2 agonists on drug craving in human participants, and their results appear to be consistent with the present experiments with respect to undesirable motor side effects.

Multiple studies have found that treatment with antipsychotic medications with action at dopamine D₂ receptors reduce cue-elicited craving in abstinent cocaine (Berger et al., 1996; De La Garza, Newton, & Kalechstein, 2005; Smelson et al., 2004) and cigarette users (see Matthews, Wilson, & Mitchell, 2011; but see Mahler & de Wit, 2005). However, atypical antipsychotic drugs are typically favored in this research (Hutchison et al., 2004; Rohsenow et al., 2008) because traditional antipsychotics with higher affinities for dopamine D₂ receptors (e.g., haloperidol) tend to produce greater motor disturbances, making their use less practical (see Shirzadi & Ghaemi, 2006).

There is also evidence that α_2 agonists have therapeutic value with regard to craving induced by cues, as well as stress. Sinha, Kimmerling, Doebrick, and Kosten (2007) reported that lofexidine lowers opioid cravings when opioid-dependent patients are read scripts about personal stressful experiences or stories about people, places, or objects related to opioid use. Sinha and colleagues also found that lofexidine increased abstinence rates in these patients. Similarly, Jobes et al. (2011) found that clonidine lowered cocaine craving in response to hearing scripts about stressful events and drug cues. However, they reported that clonidine had slightly differential effects on stress versus cues in that both doses tested blocked stress-induced craving, but only the higher dose blocked cue-induced craving. Thus, it would be interesting to examine the effects of α_2 agonists, as well as D₂ antagonists, during situations where alternative reinforcement is reduced and problem behaviors tend to increase (e.g., Volkert et al., 2009).

Accounts of Resurgence

Two accounts of resurgence have recently been proposed, and the results of the present study may provide some indication of which is more viable. The first is that resurgence is a form of contextual renewal (Bouton & Swartzentruber, 1991; Winterbauer & Bouton, 2010). The basis of this account is that all resurgence preparations include distinct changes in the background context during extinction and testing phases via the addition of alternative response and sources of reinforcement. Although context in renewal preparations is generally established through manipulations in olfactory, auditory, visual, and tactile stimuli (see Crombag et al., 2008), Winterbauer and Bouton suggest that context may be established by actions, as well as their consequences. This account suggests that resurgence is largely cue or context driven.

Podlesnik and colleagues (2006) and Quick et al. (2011) have offered an alternative account based on parallels drawn between the reinforcer loss used to induce drug seeking within the procedure and situations such as job loss or divorce that tend to produce relapse in human drug users (Falba et al., 2005; Gallo et al., 2001; San Jose et al., 2000; Temple et al., 1991). These, and similar situations, are typically considered stressful (see Sinha, 2008); therefore, resurgence could be an instance of stress-induced relapse to drug seeking.

Given the results of the present studies, the context-driven account seems most viable. Both raclopride and clonidine effectively suppressed resurgence; however, raclopride has repeatedly failed to affect stress-induced drug seeking

(Capriles et al., 2003; Shaham & Stewart, 1996; Tobin et al., 2009), whereas there is some evidence that clonidine plays a role in cue-induced drug seeking (Smith & Aston-Jones, 2011). However, these accounts of resurgence are not necessarily mutually exclusive.

There is evidence in the basic literature that common neural mechanisms mediate stress- and cue-induced reinstatement. Smith and Aston-Jones (2011) found that administration of an α_2 agonist was effective in attenuating reinstatement via cues and stress, but also that administration of a CRF₁ antagonist had the same effects. Much like the α_2 receptor, the CRF₁ receptor is generally implicated in stress-induced relapse to drug seeking (see Shalev, Erb, & Shaham, 2010), but also appears to be involved in reinstatement via drug cues (Goeders & Clampitt, 2002). As noted earlier, similar findings have been reported in human studies (Jobes et al., 2011; Sinha et al., 2007). Stress and drugs cues have also been shown to produce comparable levels of drug craving, as well as comparable physiological responses in human drug users (Sinha, Fuse, Aubin, & O'Malley, 2000). Furthermore, results of imaging studies in humans indicate that overlapping areas of the brain are activated during stress and cue exposure (see Sinha & Li, 2007). While not necessarily evidence of overlap, some animal studies have shown that reinstatement via cues and stressors together is greater than either alone (Buffalari & See, 2009, 2011; Feltenstein & See, 2006; Liu & Weiss, 2002a). Thus, there is evidence that these systems may overlap or interact with one another.

Limitations and Future Directions

Response Types

Within the present experiments the target response was always a lever press and the alternative response was always a nose poke response. A potential criticism of the present study is that response type was confounded with whether the response was the target or alternative. There is some evidence that these response may be differentially impacted by pharmacological manipulation; however, not necessarily by the drugs examined in the present experiments.

Gerhardt and Liebman (1981) tested the effects of various drugs on lever pressing and nose poking maintained by contingent brain stimulation. Among the drugs examined were clonidine (α_2 agonist) and haloperidol (D_2 -like antagonist). Although Gerhardt and Liebman reported that the nose poke response was less susceptible to disruption than the lever press under some of the drugs tested, neither clonidine nor haloperidol produced differential disruption. While these results suggest that confounding response type with assignment to target versus alternative may not be of concern, it is worth noting that Gerhardt and Liebman examined the effects of these drugs on continuous reinforcement (i.e., fixed ratio 1) of ongoing behavior rather than relapse to drug seeking or extinction of responding with a history of intermittent reinforcement. Future studies might counterbalance response type across the target and alternative responses, or use two responses that are not as readily emitted by rats (e.g., lever press and chain pull).

Measures of Motor Impairment

The present experiments examined a number of measures that have been used previously to dissociate the effects of motor and motivational impairment (Alleweireldt et al., 2002; Grimm et al., 2011; Quick et al., 2011). Although the results of these analyses were relatively unambiguous in Experiment 2, the results of Experiment 1 are more difficult to interpret. These measures gave little indication of motor impairment in 50 µg/kg raclopride group within the first Phase III session, but responding was significantly suppressed across Phase III sessions, especially with respect to the alternative poke. These results further highlight the difficulties of dissociating motivational and motor effects as described by Grimm et al. (2011).

However, other additional measures have also been used to dissociate motivational and motor drug effects, and no single study has used all of them together (see Grimm et al., 2011). Future studies could collect data on all of these measures to confirm that they converge. One such strategy is comparison of locomotor activity during drug-free sessions with activity during sessions in which the drug is administered (e.g., Grimm, Manaois, Osincup, Wells, & Buse, 2007). Locomotor activity is generally assessed with operant chambers equipped with multiple infrared emitters and detectors that arrange photo-beams across the operant chamber. Breaks in the photo-beams are then recorded and compared across sessions. A second strategy is to determine the effects of drugs on high-rate behavior maintained by food reinforcers (e.g., Erb et al., 2000). Drugs that do not impact performance of such behavior presumably leave motor performance intact.

Such tests are also important for dissociating selective impairment of drug seeking in other models of drug seeking that do not involve alternative nondrug reinforcement.

Additional Receptors

The present studies examined just two receptors that have proven to be critically involved in various other models of relapse to drug seeking, but a number of other receptors and neural systems should also be explored. In addition to dopamine D₁ and D₂ receptors, D₃ receptors have also been implicated in various models of relapse. Several studies have demonstrated that D₃ antagonists block drug-primed reinstatement (Andreoli et al., 2003; Higley et al., 2011; Khroyan et al., 2000; Peng et al., 2009; Vorel et al., 2002; Xi et al., 2006), as well as cue-induced reinstatement (Cervo, Cocco, Petrella, & Heidbreder, 2007; Gilbert et al., 2005; Khaled et al., 2010; Vengeliene et al., 2006; Weiss et al., 2001). Results are mixed with stress-induced reinstatement in that Xi et al. (2006) reported a systemic administration of a D₃ antagonist blocks shock-induced reinstatement of cocaine seeking, whereas Tobin et al. (2009) found no effect on food deprivation-induced reinstatement. Xi and colleagues also tested localized injections and found that administration in the nucleus accumbens was effective in blocking shock-induced cocaine seeking, whereas the dorsal striatum was not. Examination of D₃ antagonists on food seeking is limited, but Cervo et al. (2007) reported no effect on cue-induced reinstatement of sucrose seeking.

In addition to α_2 adrenergic receptors, previous studies have also examined various other adrenergic receptors, and these receptors are also involved in various types of relapse. For instance, administration of an α_1 antagonist blocks drug- and cue-induced (Forget et al., 2010; Zhang & Kosten, 2005), but not stress-induced reinstatement (Mantsch et al., 2010). Leri, Flores, Rodaros, and Stewart (2002) found that localized injections of a mixture of β_1 and β_2 antagonists blocks stress-induced, but not cocaine induced reinstatement. Mantsch and colleagues (2010) found parallel results in a study of reinstatement of conditioned place preference (CPP); however, the results of Mantsch et al. indicated that blockade of β_2 , but not β_1 receptors reduces stress-induced reinstatement of CPP.

A second receptor type that has received considerable attention with respect to its role in stress-induced drug seeking is the CRF₁ receptor (see Shalev et al., 2010). Systemic administration of CRF₁ antagonists attenuates shock-induced reinstatement of behavior previously maintained by a variety of drugs (Lê et al., 2000; Marinelli et al., 2007; Shaham, Erb, Leung, Buczek, & Stewart, 1998), and also food (Ghitza et al., 2006; see Nair et al., 2009). Although CRF is primarily implicated in stress-induced reinstatement, some studies have produced mixed results regarding its role in priming reinstatement, blocking it in some cases (Moffet & Goeders, 2007; Przegalinski, Filip, Frankowska, Zaniowska, & Papla, 2005), while having no effect in others (Erb, Shaham, & Stewart, 1998; Lee et al., 2003). Antagonism of CRF receptors also appears to have some effect on cue-induced reinstatement, but again, with mixed results: Systemic administration of CP-154,526

blocks cue-induced cocaine seeking (Goeders & Clampitt, 2002), but has no effect on cue-induced methamphetamine seeking (Moffett & Goeders, 2007).

The endogenous cannabinoid system may also be a potential target for future studies in that it plays important role in some types of relapse to drug seeking (see Fattore et al., 2007). For instance, blockade of these CB₁ receptors attenuates drug-primed reinstatement (De Vries et al., 2001; De Vries, Homberg, Binnekade, Raasø, & Schoffelmeer, 2003). Similar to the dopamine D₂ receptor, multiple studies have reported that administration of CB₁ antagonists decreases cue-induced reinstatement while having no effect on stress-induced reinstatement (De Vries et al., 2001; Economidou et al., 2006; but see Vaughn et al., 2012). CB₁ receptors also appear to play a role in contextual renewal of drug seeking (Diergaarde, De Vries, Raasø, Schoffelmeer, & De Vries, 2008). Furthermore, CB₁ antagonists block food-primed reinstatement (Duarte et al., 2004) and cue-induced reinstatement of food seeking (Ward, Walker, & Dystra, 2007).

Clonidine also binds with high affinity to imidazoline receptors (Ernsberger, Damon, Graff, Schäfer, & Christen, 1993). Although previous studies have suggested that it is unlikely that clonidine's action at I₁ receptors is responsible for its ability to reduce drug seeking (see Shalev et al., 2002), Smith and Aston-Jones (2011) recently reported that monoxidine, an I₁ agonist, is effective in reducing cue- and cocaine-induced reinstatement. Therefore, future studies could examine the role of I₁ receptors. It would also be of interest whether more selective α_2 agonists, such as

UK-14,304 or guanfacine (see Smith & Aston-Jones, 2011), also reduce resurgence to provide further support of the involvement of α_2 receptors.

Targeted Approaches

The present experiments examined systemic administration of raclopride and clonidine to examine the role of D_2 and α_2 receptors in resurgence, respectively. While the results of Experiments 1 and 2 provide preliminary evidence of involvement of these receptors, future studies should utilize more targeted approaches to clarify the role of these receptors, as well as gather additional information about the role of specific pathways in the brain. One of these more targeted methods is to examine the role of specific receptors using genetically modified animals that lack the receptors of interest (Spanagel & Sanchis-Segura, 2003). Animals lacking D_2 and α_2 receptors have been used in the past to study various aspects of drug taking and drug seeking (e.g., Caine et al., 2002; Wee, Mandyam, Lekic, & Koob, 2008); however, these animals also display behavioral deficits that may complicate interpretation of the results of such studies (Fowler, Zarccone, Vorontsova, & Chen, 2002; Spreng, Cotecchia, & Schenk, 2001). A second approach that aids in examination of specific pathways is to test the effects of brain lesions on behavior in animal models of relapse (e.g., Yun & Fields, 2003).

A number of previous studies have also used localized injections of different agonist and antagonist drugs into specific brain regions. Relevant to the present experiments, researchers have examined the effects of targeted administration of

dopamine D₂ antagonists and adrenergic α_2 agonists on various types of reinstatement. With respect to the stress- and context-based accounts of resurgence noted earlier, it would be most informative for future studies to examine a location in the brain that has produced differential attenuation of cue- or context-induced versus stress-induced reinstatement. That is, an area where α_2 agonists or D₂ antagonists attenuated one type of reinstatement, but not the other. Unfortunately, no previous studies have examined cue- and stress-induced drug seeking in a single area of the brain. However, this is not particularly surprising considering the overlap and interactions between these systems noted earlier (e.g., Liu & Weiss, 2002a; Sinha et al., 2000). Regardless, areas that are important in other models of relapse should still be examined.

Dopamine D₂ receptor antagonists. Dopamine D₂ antagonists injected into the nucleus accumbens shell appear to block priming reinstatement of drug-maintained behavior (Anderson, Schmidt, & Pierce, 2006; Bachtell, Whisler, Karanian, & Self, 2005), whereas administration in the nucleus accumbens core and lateral septum (Anderson et al., 2006), as well as the prelimbic prefrontal cortex (Capriles et al., 2003) does not. Administration in the dorsal prefrontal cortex attenuates reinstatement when priming injections of cocaine are combined with cocaine-paired cues (Sun & Rebec, 2005). However, injections of raclopride in the basolateral amygdala have proven ineffective in blocking cue-induced reinstatement of drug seeking (See, Kruzich, & Grimm, 2001). As noted previously, raclopride

delivered to the prelimbic cortex or orbitofrontal cortex does not block stress-induced reinstatement (Capriles et al., 2003).

Some studies have examined the effects of localized injections of D₂ antagonists on reinstatement of food seeking. The dorsal prefrontal cortex has been implicated in food-primed reinstatement (Sun & Rebec, 2005). The nucleus accumbens has been implicated in cue-induced sucrose seeking (Guy, Choi, & Pratt, 2011), but not food-primed reinstatement in a runway procedure (Chausmer & Ettenberg, 1999).

Adrenergic α_2 receptor agonists. Shaham et al. (2000) examined how inactivation of two primary clusters of adrenergic cells impacted stress-induced heroin seeking and reported that α_2 agonists injected into the locus coeruleus did not impact stress-induced reinstatement, but that selective 6-hydroxydopamine lesions to noradrenergic neurons in the lateral tegmental area reduced reinstatement without affecting extinction. Administration of α_2 agonists in the central nucleus of the amygdala also appears to block shock-induced reinstatement (Yamada & Bruijnzeel, 2011).

Conclusion

In conclusion, the present experiments shed additional light on the neuropharmacology of resurgence, implicating dopamine D₂ and adrenergic α_2 receptors. These results also provide evidence of further overlap among the popular

models of relapse, and may have implications in applied settings that employ DRA-based treatments or for human drug users in which stressful situations characterized by significant loss exacerbate drug use or induce relapse to maladaptive behaviors.

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CURRICULUM VITAE

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EDUCATION

University of Kansas, Lawrence, KS

Bachelor of General Studies, December 2006

Major: Psychology

Bachelor of General Studies, December 2006

Major: Applied Behavioral Science

Emphasis: Early Childhood Research & Education

Utah State University, Logan, UT

Master of Science, 2011

Major: Psychology

Emphasis: Experimental Analysis of Behavior

Thesis: Nondrug reinforcement loss and relapse to alcohol seeking in another context

Doctor of Philosophy, 2013

Major: Psychology

Emphasis: Experimental Analysis of Behavior

Dissertation: Selected neuropharmacology of resurgence

ORGANIZATIONAL SERVICE

Program representative for Utah State University

Association for Behavior Analysis International

2008

Student representative for Experimental & Applied Psychological Sciences subprogram

Utah State University Psychology Department

Fall 2010 - Spring 2011

AWARDS

Vice President for Research Fellowship

Utah State University, 2007

MEMBERSHIP

Association for Behavior Analysis International
 Society for Quantitative Analyses of Behavior
 Society for the Teaching of Psychology (STP/APA Division 2)

TEACHING

Utah State University
 PSY 3500, Scientific Thinking & Methods in Psychology
 3 sections, Spring 2012 - Spring 2013

RESEARCH

Data collection & analysis
 University of Kansas, 2004; 2006
 Laboratory technician
 University of Kansas, 2006
 Research Assistant: "Behavioral Momentum of Alcohol Self-Administration"
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 National Institute on Alcohol Abuse and Alcoholism
 Proposed Project Dates 04/01/08 – 03/31/13
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TRAINING

Oral alcohol self-administration in rats
 Utah State University, 2007
 Trained by Corina Jimenez-Gomez & Timothy A. Shahan

 Intravenous jugular catheterization in rats
 Utah State University, 2008-2010
 Trained by Stacey L. Quick

PRESENTATIONS

Quick, S. L., Pyszczynski, A. D., Colston, K. A., & Shahan, T. A. (2010). Resurgence of Cocaine Seeking: Role of the Dopamine D₁ Receptors. Intermountain Research Symposium, Logan UT.

Quick, S. L., Pyszczynski, A. D., Colston, K. A., & Shahan, T. A. (2010). Resurgence of cocaine seeking by removal of a non-drug alternative reinforcer. In A. Doughty (Chair), Extinction- Induced Resurgence: Some New Findings. Symposium conducted at the 36th annual meeting of the Association for Behavior Analysis International, San Antonio, TX.

Pyszczynski, A. D. & Shahan, T. A. (2010). Discontinuation of food reinforcers in one context produces recovery of extinguished alcohol-maintained responding in

a separate context. In C. Cancado, Resurgence: Controlling Variables and Implications for the Analysis of Behavior. Symposium conducted at the 36th annual meeting of the Association for Behavior Analysis International, San Antonio, TX.

POSTERS

Brewer, A. T., Johnson, P. S., Pyszczynski, A. D., Stein, J. F., Smith, N. G., Wu, H., Madden, G. J., Woods, J., Pinkston, J. W., & Williams, D. C. (2007 May). Preliminary effects of Pramipexole on choice for differential rewards in a delay discounting paradigm. Association for Behavior Analysis, San Diego CA.

Pyszczynski, A. D., & Shahan, T. A. (2008 May). Multiple-Schedule contrast and cross-context recovery of extinguished responding previously maintained by a qualitatively different reinforcer. Society for Quantitative Analysis of Behavior, Chicago IL.

Pyszczynski, A. D., & Shahan, T. A. (2010 March). Nondrug reinforcement in a context reduces rats' alcohol seeking but increases relative relapse in that context. Intermountain Research Symposium, Logan UT.

Pyszczynski, A. D., & Shahan, T. A. (2010 April). Response-independent, nondrug reinforcement reduces rats' alcohol seeking but increases relative relapse. Four Corners Association for Behavior Analysis, Park City UT.

Pyszczynski, A. D., & Shahan, T. A. (2010 May). Effects of alcohol concentration on resistance to extinction and reinstatement of alcohol self-administration. Society for Quantitative Analysis of Behavior, San Antonio TX.

PUBLICATIONS

In Preparation

Pyszczynski, A. D., & Shahan, T. A. Effects of alcohol concentration on resistance to extinction and reinstatement of alcohol self-administration.

Pyszczynski, A. D., & Shahan, T. A. Effects of added nondrug reinforcement on alcohol seeking: Food delivered contingent on a separate response and withholding a target response.

Pyszczynski, A. D., & Shahan, T. A. Selected neuropharmacology of resurgence.

In Press

Pyszczynski, A. D., & Shahan, T. A. Loss of non-drug reinforcement produces alcohol seeking in another context. (2013). *Behavioral Pharmacology*

Peer-Reviewed Articles in Print

Pyszczynski, A. D., & Shahan, T. A. (2011). Behavioral momentum and relapse of ethanol seeking: Nondrug reinforcement in a context increases relative reinstatement. *Behavioral Pharmacology, 22*, 81-86.

Quick, S. L., Pyszczynski, A. D., Colston, K. A., & Shahan, T. A. (2011). Loss of alternative non-drug reinforcement induces relapse of cocaine-seeking in rats: Role of dopamine D1 receptors. *Neuropsychopharmacology, 36*, 1015-1020.